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(54) Title: POLYCYCLIC PYRIMIDINES AS POTASSIUM ION CHANNEL MODULATORS

(57) Abstract: The present invention provides a genus of polycyclic pyrimidines that are useful as modulators of potassium ion channels. The modulators of the invention are of use in both therapeutic and diagnostic methods.



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POLYCYCLIC PYRIMIDINES AS POTASSIUM ION CHANNEL MODULATORS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Patent Application No. 60/561,990, filed April 13, 2004, which is incorporated herein by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] Ion channels are cellular proteins that regulate the flow of ions, including calcium, potassium, sodium and chloride into and out of cells. These channels are present in all human cells and affect such physiological processes as nerve transmission, muscle contraction, cellular secretion, regulation of heartbeat, dilation of arteries, release of insulin, and regulation of renal electrolyte transport. Among the ion channels, potassium ion channels are the most ubiquitous and diverse, being found in a variety of animal cells such as nervous, muscular, glandular, immune, reproductive, and epithelial tissue. These channels allow the flow of potassium in and/or out of the cell under certain conditions. For example, the outward flow of potassium ions upon opening of these channels makes the interior of the cell more negative, counteracting depolarizing voltages applied to the cell. These channels are regulated, *e.g.*, by calcium sensitivity, voltage-gating, second messengers, extracellular ligands, and ATP-sensitivity.

[0003] Potassium ion channels are typically formed by four alpha subunits, and can be homomeric (made of identical alpha subunits) or heteromeric (made of two or more distinct types of alpha subunits). In addition, certain potassium ion channels (those made from Kv, KQT and Slo or BK subunits) have often been found to contain additional, structurally distinct auxiliary, or beta subunits. These subunits do not form potassium ion channels themselves, but instead they act as auxiliary subunits to modify the functional properties of channels formed by alpha subunits. For example, the Kv beta subunits are cytoplasmic and are known to increase the surface expression of Kv channels and/or modify inactivation kinetics of the channel (Heinemann *et al.*, *J. Physiol.* **493**: 625-633 (1996); Shi *et al.*, *Neuron* **16**(4): 843-852 (1996)). In another example, the KQT family beta subunit, minK, primarily changes activation kinetics (Sanguinetti *et al.*, *Nature* **384**: 80-83 (1996)).

[0004] The alpha subunits of potassium ion channels fall into at least 8 families, based on predicted structural and functional similarities (Wei *et al.*, *Neuropharmacology* **35**(7): 805-829 (1997)). Three of these families (Kv, eag-related, and KQT) share a common motif of six transmembrane domains and are primarily gated by voltage. Two other families, CNG and SK/IK, also contain this motif but are gated by cyclic nucleotides and calcium, respectively. Small (SK) and intermediate (IK) conductance calcium-activated potassium ion channels possess unit conductances of 2-20 and 20-85 pS, respectively, and are more sensitive to calcium than are BK channels discussed below. For a review of calcium-activated potassium channels see Latorre *et al.*, *Ann. Rev. Phys.* **51**: 385-399 (1989).

[0005] Three other families of potassium channel alpha subunits have distinct patterns of transmembrane domains. Slo or BK family potassium channels have seven transmembrane domains (Meera *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **94**(25): 14066-14071 (1997)) and are gated by both voltage and calcium or pH (Schreiber *et al.*, *J. Biol. Chem.* **273**: 3509-3516 (1998)). Slo or BK potassium ion channels are large conductance potassium ion channels found in a wide variety of tissues, both in the central nervous system and periphery. These channels are gated by the concerted actions of internal calcium ions and membrane potential, and have a unit conductance between 100 and 220 pS. They play a key role in the regulation of processes such as neuronal integration, muscular contraction and hormone secretion. They may also be involved in processes such as lymphocyte differentiation and cell proliferation, spermatocyte differentiation and sperm motility. Members of the BK (Atkinson *et al.*, *Science* **253**: 551-555 (1991); Adelman *et al.*, *Neuron* **9**: 209-216 (1992); Butler, *Science* **261**: 221-224 (1993)) subfamily have been cloned and expressed in heterologous cell types where they recapitulate the fundamental properties of their native counterparts. Finally, the inward rectifier potassium channels (Kir), belong to a structural family containing two transmembrane domains, and an eighth functionally diverse family (TP, or "two-pore") contains two tandem repeats of this inward rectifier motif.

[0006] Each type of potassium ion channel shows a distinct pharmacological profile. These classes are widely expressed, and their activity hyperpolarizes the membrane potential. Potassium ion channels have been associated with a number of physiological processes, including regulation of heartbeat, dilation of arteries, release of insulin, excitability of nerve cells, and regulation of renal electrolyte transport. Moreover, studies have indicated that potassium ion channels are a therapeutic target in the treatment of a number of diseases including central or peripheral nervous system disorders (*e.g.*, migraine,

ataxia, Parkinson's disease, bipolar disorders, trigeminal neuralgia, spasticity, mood disorders, brain tumors, psychotic disorders, myokymia, seizures, epilepsy, hearing and vision loss, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, age-related memory loss, learning deficiencies, anxiety, traumatic brain injury, dysmenorrhea, narcolepsy and motor neuron diseases), as well as targets for neuroprotective agents (*e.g.*, to prevent stroke and the like); as well as disease states such as gastroesophageal reflux disorder and gastrointestinal hypomotility disorders, irritable bowel syndrome, secretory diarrhea, asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, ischemia, cerebral ischemia, ischemic heart disease, angina pectoris, coronary heart disease, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, arrhythmia, hypertension, myotonic muscle dystrophia, xerostomia, diabetes type II, hyperinsulinemia, premature labor, baldness, cancer, and immune suppression.

[0007] Specifically, SK channels have been shown to have distinct pharmacological profiles. For example, using patch clamp techniques, the effects of eight clinically relevant psychoactive compounds on SK2 subtype channels were investigated (Dreixler *et al.*, *Eur. J. Pharmacol.* **401**: 1-7 (2000)). The evaluated compounds are structurally related to tricyclic antidepressants and include amitriptyline, carbamazepine, chlorpromazine, cyproheptadine, imipramine, tacrine and trifluperazine. Each of the compounds tested was found to block SK2 channel currents with micromolar affinity. A number of neuromuscular inhibiting agents exist that affect SK channels, *e.g.* apamin, atracurium, pancuronium and tubocurarine (Shah *et al.*, *Br J Pharmacol* **129**: 627-30 (2000)).

[0008] Moreover, patch clamp techniques have also been used to study the effect of the centrally acting muscle relaxant chlorzoxazone and three structurally related compounds, 1-ethyl-2-benzimidazolinone (1-EBIO), zoxazolamine, and 1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-benzimidazol-2-one (NS 1619) on recombinant rat brain SK2 channels (rSK2 channels) expressed in HEK293 mammalian cells (Cao *et al.*, *J Pharmacol. Exp. Ther.* **296**: 683-689 (2001)). When applied externally, chlorzoxazone, 1-EBIO, and zoxazolamine activated rSK2 channel currents in cells dialyzed with a nominally calcium-free intracellular solution.

[0009] The effects of metal cations on the activation of recombinant human SK4 (also known as hIK1 or hKCa4) channels has also been studied (Cao and Houamed, *FEBS Lett.* 446: 137-41 (1999)). The ion channels were expressed in HEK 293 cells and tested using patch clamp recording. Of the nine metals tested, cobalt, iron, magnesium, and zinc did not activate the SK4 channels when applied to the inside of SK4 channel-expressing membrane patches. Barium, cadmium, calcium, lead, and strontium activated SK4 channels in a concentration-dependent manner. Calcium was the most potent metal, followed by lead, cadmium, strontium, and barium.

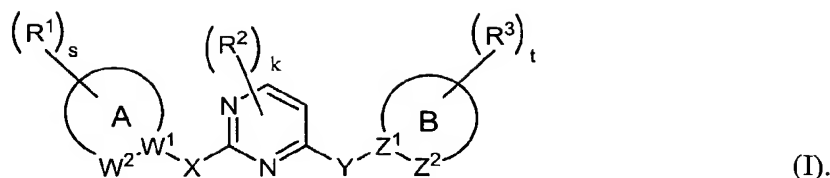
[0010] The SK channels are heteromeric complexes that comprise pore-forming α -subunits and the calcium binding protein calmodulin (CaM). CaM binds to the SK channel through the CaM-binding domain (CaMBD), which is located in an intracellular region of an α -subunit close to the pore. Based on a recently published crystal structure, calcium binding to the N-lobe of the CaM proteins on each of the four subunits initiates a structural change that allows a hydrophobic portion of the CaM protein to interact with a CaMBD on an adjacent subunit. As each N-lobe on an adjacent subunit grabs the other CaMBD C-terminal region, a rotary force is thought to be created between them which would drive open the channel.

[0011] New classes of compounds that act to modulate the opening of potassium ion channels would represent a significant advance in the art and provide the opportunity to develop treatment modalities for numerous diseases associated with these channels. The present invention provides a new class of potassium ion channel modulators and methods of using the modulators.

BRIEF SUMMARY OF THE INVENTION

[0012] The present invention provides polycyclic pyrimidines, prodrugs, complexes, and pharmaceutically acceptable salts thereof, which are useful in the treatment of diseases through the modulation of potassium ion flow through potassium ion channels.

[0013] In a first aspect, the potassium ion channel modulator is a compound according to Formula I:



In Formula (I), A and B are independently substituted or unsubstituted 5- or 6- membered heterocycloalkyl or substituted or unsubstituted 5- or 6- membered heteroaryl. The symbol

W^1 is $\begin{array}{c} \text{---C=} \\ | \end{array}$ or $\begin{array}{c} \text{---N---} \\ | \end{array}$. W^2 is -CH=, -NH-, -N=, or -O-. The symbol Z^1 is $\begin{array}{c} \text{---C=} \\ | \end{array}$, $\begin{array}{c} \text{---N---} \\ | \end{array}$, or $\begin{array}{c} \oplus \\ \text{---N---} \\ || \end{array}$. Z^2 is -CH=, -NH-, -N=, or -O-. The symbol X is a bond, -CH₂-, or -NR⁴-. Y is a bond, -CH=N-NH-, -NH-CH₂-, or -NR⁵-.

[0014] The symbols s and t are independently integers from 1 to 4.

[0015] The symbol k is an integer from 1 to 2.

[0016] R¹, R², and R³ are independently H, -OH, -NH₂, -NO₂, -SO₂NH₂, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 3- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or -NR⁷R⁸.

[0017] R⁷ and R⁸ are independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 5- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R⁷ and R⁸ are optionally joined together with the nitrogen to which they are attached to form a substituted or unsubstituted 5- to 7- membered heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[0018] R⁴ and R⁵ are independently H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 3- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0019] Where a plurality of R¹, R², and/or R³ groups are present, each R¹, R², and/or R³ is optionally different.

[0020] R¹, R², and R³ may optionally form part of a fused ring system.

[0021] In a second aspect, the present invention provides a method for decreasing ion flow through potassium ion channels in a cell, comprising contacting the cell with a potassium ion channel modulating amount of a modulator of the present invention.

[0022] In a third aspect, the present invention provides a method for treating a disease through the modulation of potassium ion flow through potassium ion channels. The modulators are useful in the treatment of central or peripheral nervous system disorders (*e.g.*, migraine, ataxia, Parkinson's disease, bipolar disorders, trigeminal neuralgia, spasticity, mood disorders, brain tumors, psychotic disorders, myokymia, seizures, epilepsy, hearing and vision loss, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, age-related memory loss, learning deficiencies, anxiety, traumatic brain injury, dysmenorrhea, narcolepsy and motor neuron diseases), and as neuroprotective agents (*e.g.*, to prevent stroke and the like). The modulators of the invention are also useful in treating disease states such as gastroesophageal reflux disorder and gastrointestinal hypomotility disorders, irritable bowel syndrome, secretory diarrhea, asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, ischemia, cerebral ischemia, ischemic heart disease, angina pectoris, coronary heart disease, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, arrhythmia, hypertension, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labor, baldness, cancer, and immune suppression. This method involves administering, to a patient, an effective amount of a modulator of the present invention.

[0023] In a fourth aspect, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a modulator of the present invention.

[0024] These and other aspects and embodiments of the invention will be apparent from the detailed description that follows.

DETAILED DESCRIPTION OF THE INVENTION

I. Abbreviations and Definitions

[0025] The abbreviations used herein have their conventional meaning within the chemical and biological arts.

[0026] Where moieties are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, -CH₂O- is equivalent to -OCH₂-.

[0027] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C₁-C₁₀ or 1- to 10-membered means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below, such as "heteroalkyl." Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl".

[0028] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified, but not limited, by -CH₂CH₂CH₂CH₂-, and further includes those groups described below as "heteroalkylene." Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0029] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0030] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder

of the molecule. Examples include, but are not limited to, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{C}(=\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}(=\text{O})-\text{O}-\text{C}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}(=\text{O})-\text{N}-\text{CH}(\text{CH}_3)$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'$ represents both $-\text{C}(\text{O})_2\text{R}'$ and $-\text{R}'\text{C}(\text{O})_2-$.

[0031] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Thus, a cycloalkyl or heterocycloalkyl include saturated and unsaturated ring linkages. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0032] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C₁-C₄)alkyl" is meant to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0033] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (preferably from 1 to 3 rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule

through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0034] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0035] The term "oxo" as used herein means an oxygen that is double bonded to a carbon atom.

[0036] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0037] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'', R''' and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, *e.g.*, aryl substituted with 1 to 3 halogens, substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a modulator of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these

groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0038] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: halogen, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''' and R'''' are preferably independently selected from hydrogen, alkyl, heteroalkyl, aryl and heteroaryl. When a modulator of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present.

[0039] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CRR')_s-X-(CR''R''')_d-, where s and d are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituents R, R', R'' and R''' are preferably independently selected from hydrogen or substituted or unsubstituted (C₁-C₆)alkyl.

[0040] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0041] A "substituent group," as used herein, means a group selected from the following moieties:

[0042] (A) -OH, -NH₂, -SH, -CN, -CF₃, oxy, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0043] (B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0044] (i) oxy, -OH, -NH₂, -SH, -CN, -CF₃, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0045] (ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0046] (a) oxy, -OH, -NH₂, -SH, -CN, -CF₃, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0047] (b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from oxy, -OH, -NH₂, -SH, -CN, -CF₃, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0048] A "size-limited substituent" or "size-limited substituent group," as used herein means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2- to 20- membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl.

[0049] A "lower substituent" or "lower substituent group," as used herein means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each

substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₅-C₇ cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

[0050] The term "pharmaceutically acceptable salts" is meant to include salts of the active modulators which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the modulators described herein. When modulators of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such modulators with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When modulators of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such modulators with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see, for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science* **66**: 1-19 (1977)). Certain specific modulators of the present invention contain both basic and acidic functionalities that allow the modulators to be converted into either base or acid addition salts.

[0051] The neutral forms of the modulators are preferably regenerated by contacting the salt with a base or acid and isolating the parent modulator in the conventional manner. The parent form of the modulator differs from the various salt forms in certain physical properties, such as solubility in polar solvents.


[0052] In addition to salt forms, the present invention provides modulators, which are in a prodrug form. Prodrugs of the modulators described herein are those compounds or complexes that readily undergo chemical changes under physiological conditions to provide the modulators of the present invention. Additionally, prodrugs can be converted to the

modulators of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the modulators of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0053] The term "ring" as used herein means a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. A ring includes fused ring moieties. The number of atoms in a ring are typically defined by the number of members in the ring. For example, a "5- to 7- membered ring" means there are 5-7 atoms in the encircling arrangement. The ring optionally includes a heteroatom. Thus, the term "5- to 7- membered ring" includes, for example pyridinyl, piperidinyl and thiazolyl rings.

[0054] The term "poly" as used herein means at least 2. For example, a polyvalent metal ion is a metal ion having a valency of at least 2.

[0055] "Moiety" refers to the radical of a molecule that is attached to another moiety.

[0056] The symbol , whether utilized as a bond or displayed perpendicular to a bond indicates the point at which the displayed moiety is attached to the remainder of the molecule.

[0057] Certain modulators of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain modulators of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

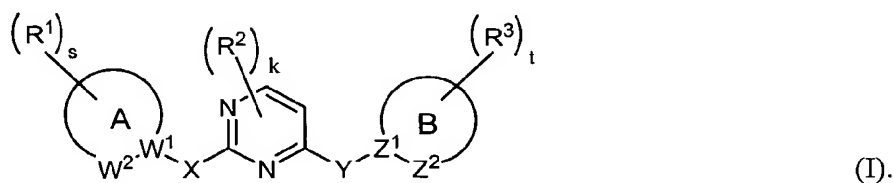
[0058] Certain modulators of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are encompassed within the scope of the present invention.

[0059] The modulators of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such modulators. For example, the modulators may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the modulators of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

II. Potassium Ion Channel Modulators

[0060] The invention provides potassium ion channel modulators that include a pyrimidinyl moiety and a first and a second ring, each of said rings being attached, either directly or through a linker, to the pyrimidinyl moiety. A potassium ion channel modulator of the present invention ("modulator of the present invention") may be a compound (also referred to herein as a "compound of the present invention") or metal ion complex (also referred to herein as a "complex of the present invention"), as described below.

[0061] In one aspect, the potassium ion channel modulator is a compound according to Formula (I):



In Formula (I), A and B are independently substituted or unsubstituted 5- or 6- membered heterocycloalkyl, or substituted or unsubstituted 5- or 6- membered heteroaryl. The symbol

W^1 is $\begin{array}{c} \text{---C=} \\ | \end{array}$ or $\begin{array}{c} \text{---N---} \\ | \end{array}$. W^2 is -CH=, -NH-, -N=, or -O-. The symbol Z^1 is $\begin{array}{c} \text{---C=} \\ | \end{array}$, $\begin{array}{c} \text{---N---} \\ | \end{array}$, or $\begin{array}{c} \oplus \\ \text{---N---} \\ || \end{array}$. Z^2 is -CH=, -NH-, -N=, or -O-. The symbol X is a bond, -CH₂-, or -NR⁴-. Y is a bond, -CH=N-NH-, -NH-CH₂-, or -NR⁵-. In some embodiments, X is a bond.

[0062] The symbols s and t are independently integers from 1 to 4. One of skill in the art will immediately recognize that where A is a 5- membered heterocycloalkyl or 5- membered heteroaryl, then s is an integer from 1 to 3; and where A is a 6- membered heterocycloalkyl or 6- membered heteroaryl, then s is an integer from 1 to 4. Likewise, where B is a 5- membered heterocycloalkyl or 5- membered heteroaryl, then t is an integer from 1 to 3 and where B is a 6- membered heterocycloalkyl or 6- membered heteroaryl, then t is an integer from 1 to 4.

[0063] The symbol k is an integer from 1 to 2.

[0064] R¹, R², and R³ are independently H, -OH, -NH₂, -NO₂, -SO₂NH₂, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 3- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or -NR⁷R⁸.

[0065] R^7 and R^8 are independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 5- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^7 and R^8 are optionally joined together with the nitrogen to which they are attached to form a substituted or unsubstituted 5- to 7- membered heterocycloalkyl, or substituted or unsubstituted heteroaryl.

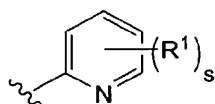
[0066] R^4 and R^5 are independently H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 3- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0067] Where a plurality of R^1 , R^2 , and/or R^3 groups are present, each R^1 , R^2 , and/or R^3 group is optionally different. For example, where s is greater than one, then each R^1 is optionally different; where k is greater than one, then each R^2 is optionally different; and where t is greater than one, then each R^3 is optionally different.

[0068] R^1 , R^2 , and R^3 may optionally form part of a fused ring system. For example, two R^1 groups are optionally joined together with the atoms to which they are attached to form a substituted or unsubstituted 5- to 7- membered ring; two R^2 groups are optionally joined together with the atoms to which they are attached to form a substituted or unsubstituted 5- to 7- membered ring; and two R^3 groups are optionally joined together with the atoms to which they are attached to form a substituted or unsubstituted 5- to 7- membered ring.

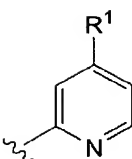
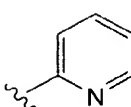
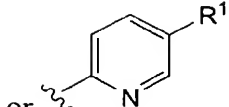
[0069] In some embodiments, A is substituted or unsubstituted heteroaryl. A may also be substituted or unsubstituted pyridinyl.

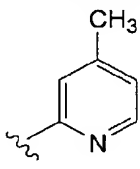
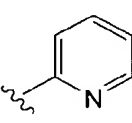
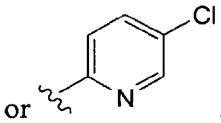
[0070] In other embodiments, A is



(III).

In Formula (III), R^1 and s are as defined above in the description of Formula (I). In some embodiments, R^1 is selected from H, halogen, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 5- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

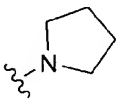
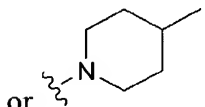
[0071] A may also be , , or . R¹ is as described above in the discussion of Formula (I) of Formula (III). Alternatively, R¹ is halogen, or substituted or unsubstituted alkyl. In a related embodiment, R¹ is Cl or unsubstituted alkyl

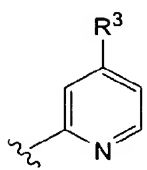
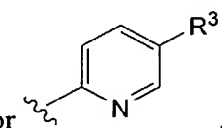
(e.g. methyl, ethyl and the like). Thus, A may , , or .

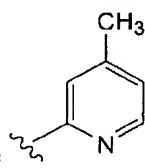
[0072] In other embodiments, B is substituted or unsubstituted heteroaryl. B may also be substituted or unsubstituted pyridinyl. Alternatively, B is



In Formula (II), R³ and t are as defined above in the description of Formula (I). In some embodiments of Formula (II), R³ is H, -NH₂, -NO₂, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 3- to 7-membered cycloalkyl, substituted or unsubstituted 5- to 7-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In another

embodiment, R³ is Cl or -NR⁷R⁸. In a related embodiment, R³ is -NH₂, -N(CH₃)₂, ,
or .

[0073] In other embodiments, B is  or . R³ is as defined above in the description of Formula (I) or Formula (II). In other embodiments, R³ is substituted or

unsubstituted alkyl (e.g. methyl, ethyl, and the like). Thus, B may be .

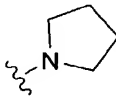
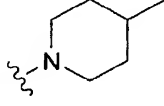
[0074] R^1 , R^2 , and R^3 may independently be H, $-NH_2$, $-NO_2$, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 3- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or $-NR^7R^8$.

[0075] Alternatively, R^1 may be H, substituted or unsubstituted (C_1 - C_{10}) alkyl, substituted or unsubstituted 2- to 10- membered heteroalkyl, or substituted or unsubstituted aryl. R^1 may also be H, methyl, $-NH_2$, or unsubstituted phenyl.

[0076] R^2 may be H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, or substituted or unsubstituted aryl. R^2 may also be H, Cl, methyl, $-OCH_3$, or unsubstituted pyridinyl. In some embodiments, R^2 is H or $-OCH_3$.

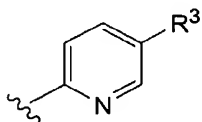
[0077] R^3 may be H, $-NH_2$, $-NO_2$, halogen, substituted or unsubstituted (C_1 - C_{10}) alkyl, substituted or unsubstituted 2- to 10- membered heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^3 may also be H, $-NH_2$, $-NO_2$, Cl, Br, F, methyl, phenyl, fluorophenyl, $-CF_3$, $-OCH_3$, dimethylamino, unsubstituted piperidine, *p*-methyl morpholino, unsubstituted pyrrolidinonyl, unsubstituted 2-thiophenyl, unsubstituted 3-thiophenyl, unsubstituted furanyl, or *n*-methyl piperizinyl.

[0078] Alternatively, R^3 is Cl or $-NR^7R^8$, where R^7 and R^8 are as defined above.

[0079] R^3 may also be selected from R^3 is Cl, $-NH_2$, $-N(CH_3)_2$, , or .

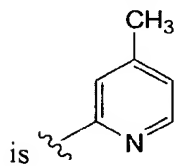
[0080] In some embodiments, X is a bond. In a related embodiment k is 2. In a further related embodiment, R^2 is H or $-OCH_3$.

[0081] In other embodiments, Y is NH. In a related embodiment, t is 1. In a further related embodiment, B is



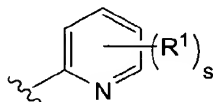
(II).

R^3 is as defined above in the description of Formula (II). In another related embodiment, B is



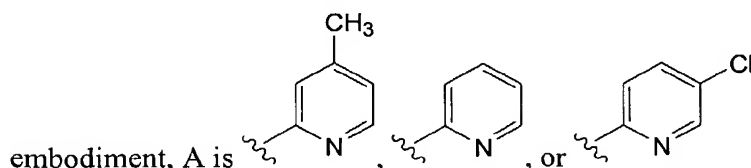
[0082] The symbol Y may also represent a bond. In a related embodiment, k is 1. In another related embodiment, R² is H.

[0083] X may be NH. In some related embodiments, A is



(III).

R¹ and s are as defined above in the description of Formula (III). In another related



embodiment, A is

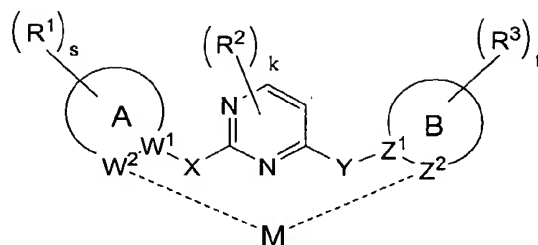
[0084] In some embodiments, each substituted moiety described above for the compounds of the present invention is substituted with at least one substituent group. The term "substituent group," as used herein, is defined in detail above in the "Abbreviations and Definitions" section. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl described above are substituted with at least one substituent group. Each substituent group is optionally different. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. Alternatively, at least one or all of these groups are substituted with at least one lower substituent group. Size-limited substituent groups and lower substituent groups are both defined in detail above in the "Abbreviations and Definitions" section.

[0085] In other embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₂₀ alkyl, and each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2- to 20- membered heteroalkyl.

[0086] Alternatively, each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, and each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2- to 8- membered heteroalkyl.

[0087] In another embodiment, the present invention provides a metal complex modulator, comprising a polyvalent metal ion (e.g. iron, zinc, copper, cobalt, manganese, and nickel) and a polydentate component of a metal ion chelator. The polydentate component is a compound of the present invention (e.g. a compound of Formulae (I), (II), or (III)). The metal complexes of the present invention are potassium ion channel modulators.

[0088] In some embodiments, the metal complex modulator has the structure



(IV).

[0089] In Formula (IV), M is a polyvalent metal ion (e.g. iron, zinc, copper, cobalt, manganese, and nickel). W^2 and Z^2 are $-N=$. W^1 , Z^1 , R^1 , R^2 , R^3 , X, Y, s, k, t, A, and B are as defined above in the description of the compound of Formula (I).

[0090] Also within the scope of the present invention are compounds of the invention that function as poly- or multi-valent species, including, for example, species such as dimers, trimers, tetramers and higher homologs of the compounds of the invention or reactive analogues thereof. The poly- and multi-valent species can be assembled from a single species or more than one species of the invention. For example, a dimeric construct can be "homo-dimeric" or "heterodimeric." Moreover, poly- and multi-valent constructs in which a compound of the invention or reactive analogues thereof are attached to an oligomeric or polymeric framework (e.g., polylysine, dextran, hydroxyethyl starch and the like) are within the scope of the present invention. The framework is preferably polyfunctional (*i.e.* having an array of reactive sites for attaching compounds of the invention). Moreover, the framework can be derivatized with a single species of the invention or more than one species of the invention.

Preparation of Potassium Ion Channel Modulators

[0091] The following exemplary schemes illustrate methods of preparing the modulators of the present invention. These methods are not limited to producing the compounds shown, but can be used to prepare a variety of modulators such as the compounds and complexes described above. The modulators of the invention can also be produced by methods not explicitly illustrated in the schemes but are well within the skill of one in the art. The modulators can be prepared using readily available starting materials or known intermediates.

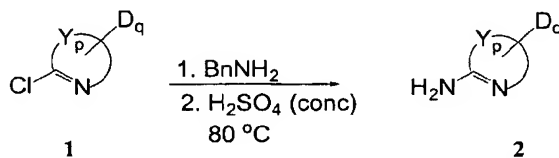
[0092] In the following schemes, the symbol Y is independently selected from CH_2 , N, S, and O. The symbol D is independently selected from H, $-OH$, $-NH_2$, $-NO_2$, $-SO_2NH_2$, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 3- to 7- membered cycloalkyl, substituted or unsubstituted 5- to

7- membered heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The symbol p is an integer independently selected from 1-5. The symbol q is an integer independently selected from 0-5.

[0093] The substituents of the pyrimidinyl compounds of the invention can be produced through the methods outlined in Schemes 1-8.

[0094] In one embodiment, the substituents of the invention comprise amino-substituted heteroaryl moieties as shown in Schemes 1-6.

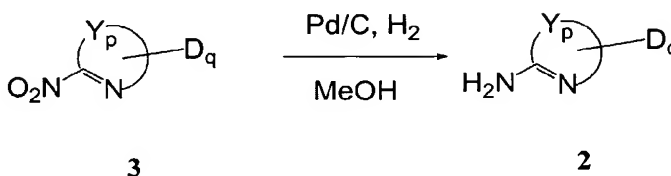
Scheme 1



[0095] In Scheme 1, compound **1** is reacted with benzylamine, followed by debenzylation in concentrated sulfuric acid to produce **2**.

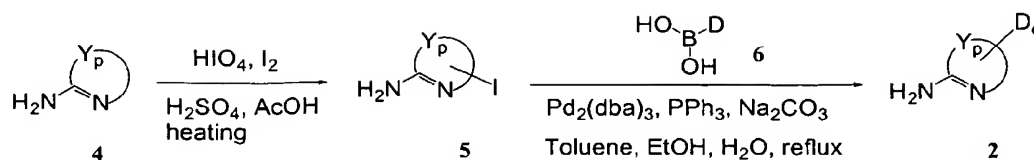
[0096] An alternative route to producing compound **2** is shown in Scheme 2.

Scheme 2



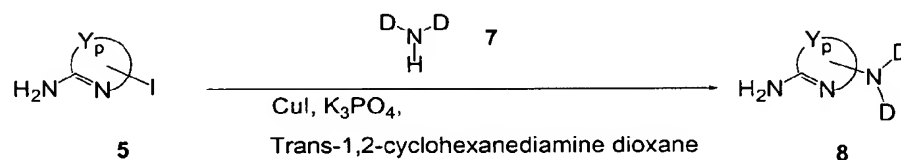
[0097] In Scheme 2, a compound **3** is reduced to form compound **2**.

[0098] Substituents can be added to the amino-substituted heteroaryl moieties as described in Schemes 3-6.

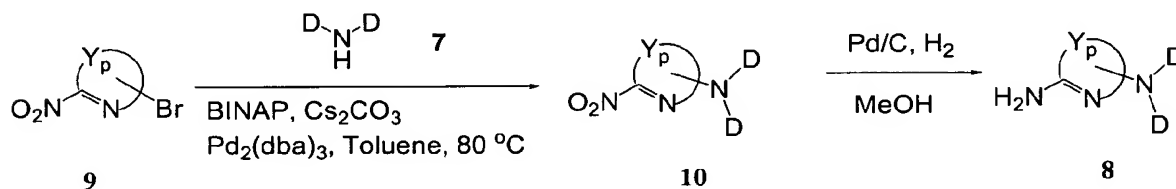
Scheme 3

[0099] In Scheme 3, compound **4** is iodinated to produce a halosubstituted 2-amino-aza-heterocycle **5**. This compound is reacted with a boronic acid **6** in the presence of tris(dibenzylideneacetone)dipalladium(0) ($\text{Pd}_2(\text{dba})_3$), and PPh_3 in toluene, ethanol, and water to produce **2**.

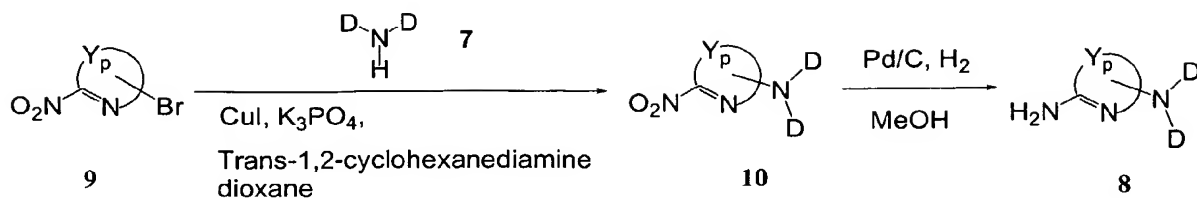
[0100] In another example, amino substituents can be added to the heteroaryl moieties in the following manner.

Scheme 4

[0101] In Scheme 4, an iodo-substituted 2-amino-aza-heterocycle **5** is reacted with an amine **7** or amide using copper catalyzed coupling chemistry to generate a 2-amino-aza-heterocycle **8**.

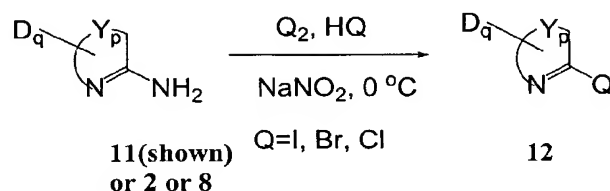
Scheme 5

[0102] In Scheme 5, a bromo-substituted 2-nitro-aza-heterocycle **9** is reacted with an amine **7** or amide using palladium-catalyzed coupling chemistry to generate an aminosubstituted 2-nitro-aza-heterocycle **10**. The nitro adduct is reduced to an amino adduct **8** by a palladium catalyzed hydrogenation.

Scheme 6

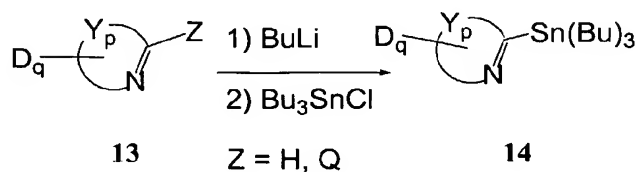
[0103] In Scheme 6, a bromo-substituted 2-nitro-aza-heterocycle **9** is reacted with an amine **7** or amide using copper catalyzed coupling chemistry to generate an aminosubstituted 2-nitro-aza-heterocycle **10**. The nitro adduct is reduced to an amino adduct **8** by a palladium catalyzed hydrogenation.

[0104] In one embodiment, the substituents of the invention comprise halo-substituted heteroaryl moieties as shown in Scheme 7.

Scheme 7

[0105] In Scheme 7, compound **11** or **2** or **8** is halogenated by diazotization followed by sodium nitrite in the presence of acid containing halogen at 0°C to produce compound **12**.

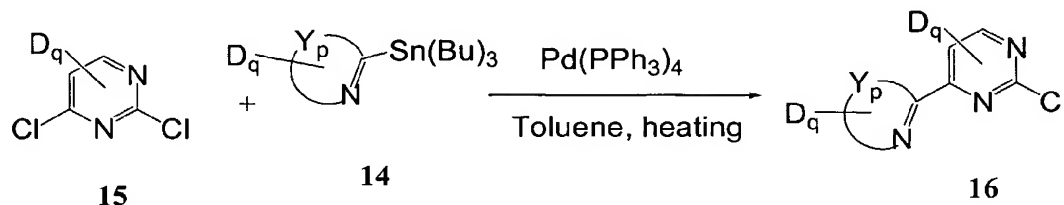
[0106] In another embodiment, the substituents of the invention comprise stannyl-substituted heteroaryl moieties as shown in Scheme 8.

Scheme 8

[0107] In Scheme 8, compound **13** is stannylated with *n*-butyllithium to produce compound **14**.

[0108] Stannyl-substituted and halo-substituted heteroaryl moieties can be added to a pyrimidine compound of the invention through the methods outlined in Scheme 9.

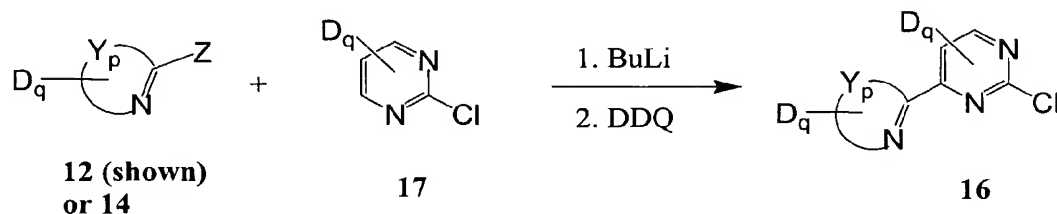
Scheme 9



[0109] In Scheme 9, addition of compound 14 to a 2,4-dichloropyrimidine 15 in the presence of a palladium catalyst in toluene produces compound 16.

[0110] An alternative way of producing compound 16 is illustrated in Scheme 10.

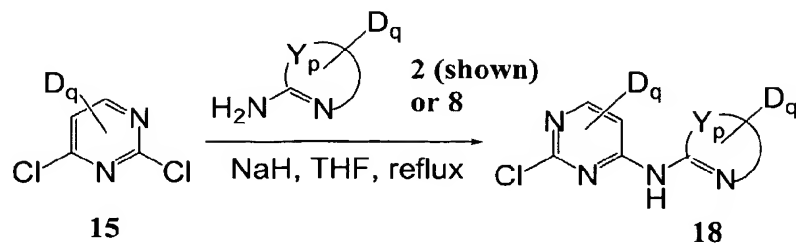
Scheme 10



[0111] In Scheme 10, compound 12 or 14 is reacted with 2-chloropyrimidine 17 in the presence of *n*-butyllithium to produce 16.

[0112] Amino-substituted heteroaryl moieties can be added to a pyrimidine compound of the invention through the methods outlined in Scheme 11.

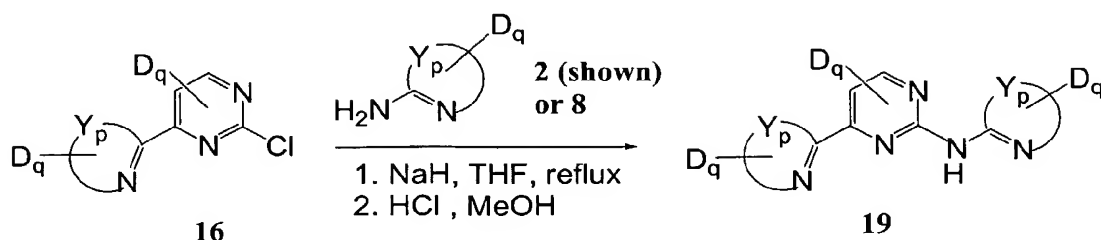
Scheme 11



[0113] In Scheme 11, compound 2 or 8 is mixed with sodium hydride to facilitate the nucleophilic addition of 2 or 8 to compound 15 to form compound 18.

[0114] Bis-substituted pyrimidines are produced from the method of Scheme 12.

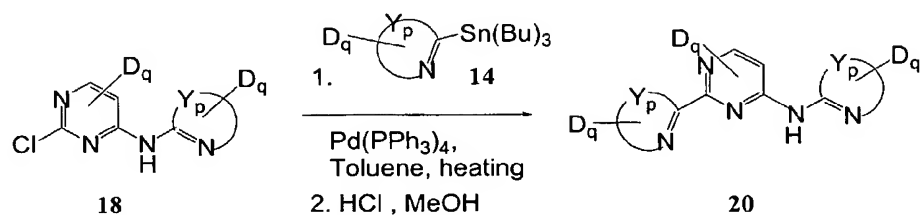
Scheme 12



[0115] In Scheme 12, compound 2 or 8 is mixed with sodium hydride to facilitate the nucleophilic addition of 2 or 8 to compound 16. The final product is a bis-substituted pyrimidine 19.

[0116] An alternative method of producing bis-substituted pyrimidine compounds of the invention is illustrated by Scheme 13.

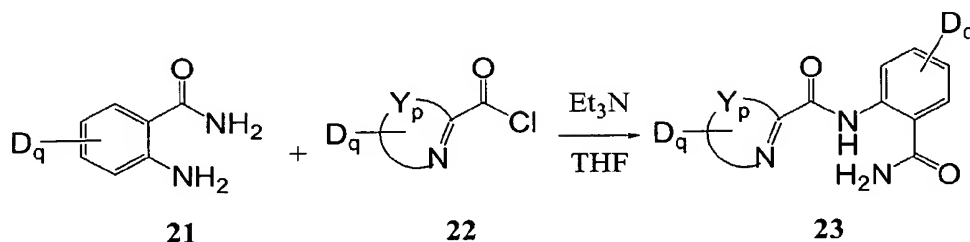
Scheme 13



[0117] In Scheme 13, compound 14 is added to compound 18 in the presence of a palladium catalyst in toluene to produce the hydrochloride salt of a bis-substituted pyrimidine 20.

[0118] A method of making substituted pyrimidines with a fused aromatic ring is described in Scheme 14.

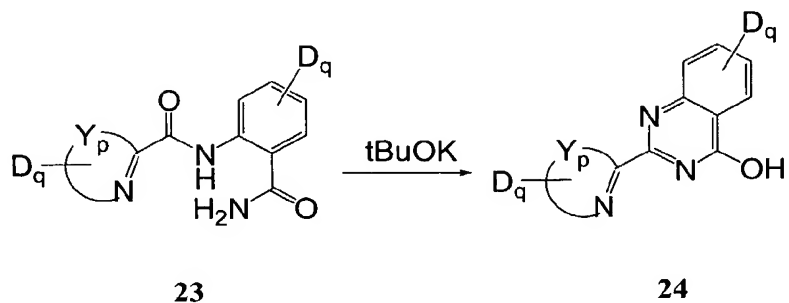
Scheme 14



[0119] In Scheme 14, compound **21** is reacted with compound **22** in the presence of triethylamine in THF to provide compound **23**.

[0120] The pyrimidine ring can be formed by a method outlined in Scheme 15.

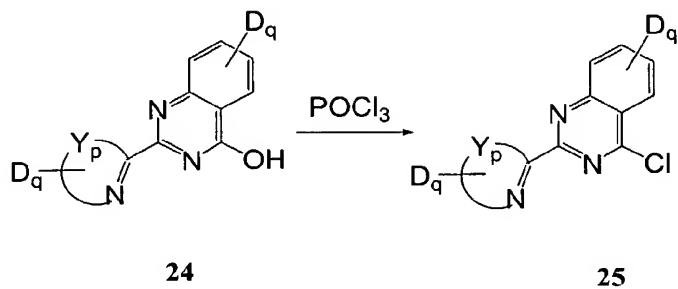
Scheme 15



[0121] In Scheme 15, addition of a base causes the intramolecular cyclization of compound **23** to form compound **24**.

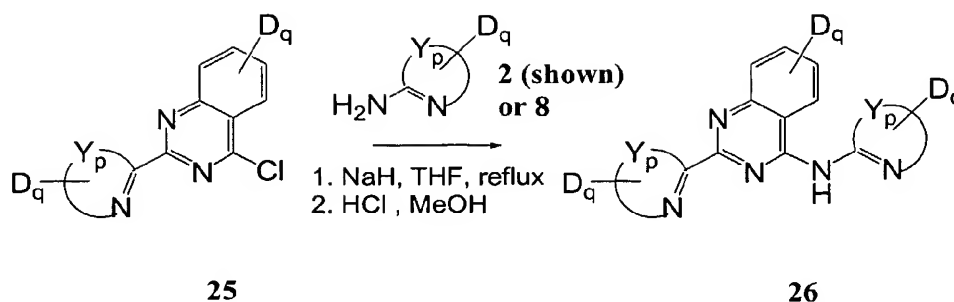
[0122] The OH at the 4-position of the pyrimidine ring can be converted into a chlorine by the procedure outlined in Scheme 16.

Scheme 16



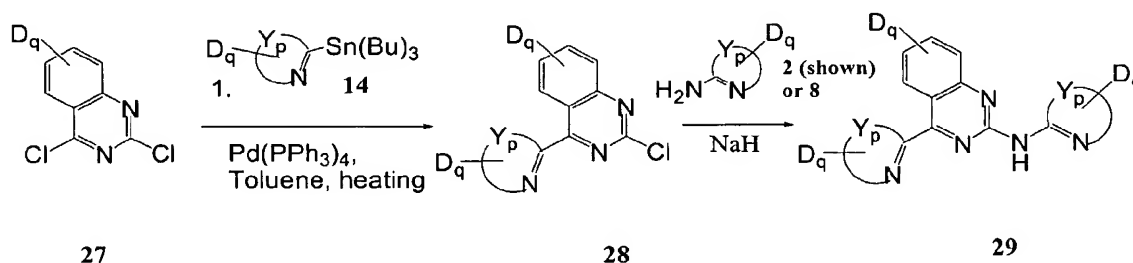
[0123] In Scheme 16, compound **24** is reacted with phosphorus oxychloride in order to produce compound **25**.

[0124] A new substituent can be added to the 4-position of the pyrimidine ring as shown in Scheme 17.

Scheme 17

[0125] In Scheme 17, compound **2** or **8** is mixed with sodium hydride to facilitate the nucleophilic addition of **2** or **8** to compound **25**. The product is a bis-substituted pyrimidine **26**.

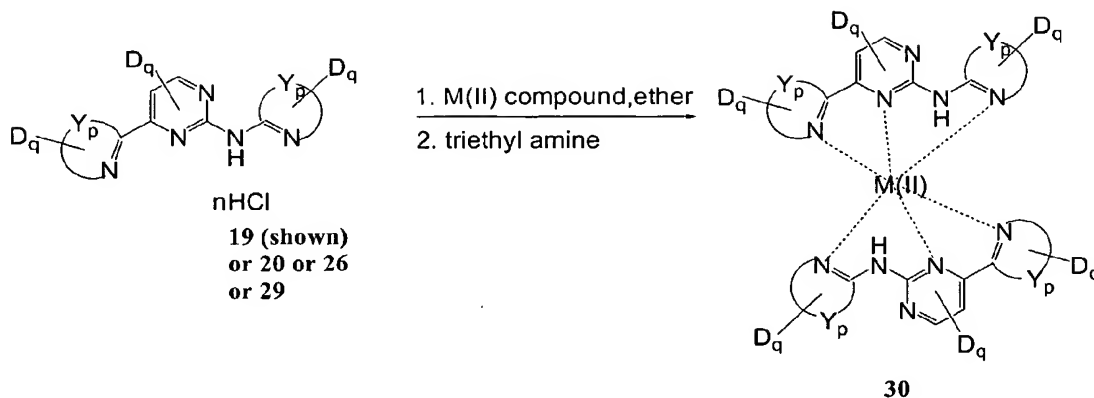
[0126] An alternative method of making substituted pyrimidines with a fused aromatic ring is described in Scheme 18.

Scheme 18

[0127] Compound **27** is reacted with stannyl derivative **14** in order to produce compound **28**. Compound **28** is then reacted with compound **2** or **8**. The product is a bis-substituted pyrimidine **29**.

[0128] The compounds of the invention also include metal complexes. These metal complexes comprise a polyvalent metal ion and a pyrimidinyl compound of the invention. In an exemplary embodiment, the polyvalent metal ion can be a transition metal. In another exemplary embodiment, the polyvalent metal ion is a member selected from iron, zinc, copper, cobalt, manganese, and nickel.

[0129] A method of creating metal-pyrimidinyl complexes of the invention is outlined in Scheme 19.

Scheme 19

[0130] In Scheme 19, compound 19 or 20 or 26 or 29, or combinations thereof, are first mixed with $FeClO_4$ in ether. To this mixture is added triethylamine which then forms metal complex 30.

III. Assays for Modulators of Potassium Ion Channels

[0131] SK monomers as well as SK alleles and polymorphic variants are subunits of potassium ion channels. The activity of a potassium ion channel comprising SK subunits can be assessed using a variety of *in vitro* and *in vivo* assays, *e.g.*, measuring current, measuring membrane potential, measuring ion flow, *e.g.*, potassium or rubidium, measuring potassium concentration, measuring second messengers and transcription levels, using potassium-dependent yeast growth assays, and using *e.g.*, voltage-sensitive dyes, radioactive tracers, and patchClamp electrophysiology.

[0132] Furthermore, such assays can be used to test for inhibitors and activators of channels comprising SK. The SK family of channels is implicated in a number of disorders that are targets for a therapeutic or prophylactic regimen, which functions by blockade or inhibition of one or more members of the SK channel family. The modulators and methods of the invention are useful to treat central or peripheral nervous system disorders (*e.g.*, migraine, ataxia, Parkinson's disease, bipolar disorders, trigeminal neuralgia, spasticity, mood disorders, brain tumors, psychotic disorders, myokymia, seizures, epilepsy, hearing and vision loss, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, age-related memory loss, learning deficiencies, anxiety, traumatic brain injury, dysmenorrhea, narcolepsy and motor neuron diseases). The modulators of the invention are also useful in treating disease states such as gastroesophageal reflux disorder

and gastrointestinal hypomotility disorders, irritable bowel syndrome, secretory diarrhea, asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, ischemia, cerebral ischemia, ischemic heart disease, angina pectoris, coronary heart disease, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, arrhythmia, hypertension, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labor, baldness, cancer, and immune suppression.

[0133] Modulators of the potassium ion channels are tested using biologically active SK, either recombinant or naturally occurring, or by using native cells, like cells from the nervous system expressing an SK channel. SK channels can be isolated, co-expressed or expressed in a cell, or expressed in a membrane derived from a cell. In such assays, SK is expressed alone to form a homomeric potassium ion channel or is co-expressed with a second subunit (*e.g.*, another SK family member) so as to form a heteromeric potassium ion channel. Modulation is tested using one of the *in vitro* or *in vivo* assays described above. Samples or assays that are treated with a potential potassium ion channel inhibitor or activator are compared to control samples without the test modulator, to examine the extent of modulation. Control samples (untreated with activators or inhibitors) are assigned a relative potassium ion channel activity value of 100. Inhibition of channels comprising SK is achieved when the potassium ion channel activity value relative to the control is less than 70%, preferably less than 40% and still more preferably, less than 30%. Modulators that decrease the flow of ions will cause a detectable decrease in the ion current density by decreasing the probability of a channel comprising SK being open, by decreasing conductance through the channel, and decreasing the number or expression of channels.

[0134] Changes in ion flow may be assessed by determining changes in polarization (*i.e.*, electrical potential) of the cell or membrane expressing the potassium ion channel. A preferred means to determine changes in cellular polarization is by measuring changes in current or voltage with the voltageClamp and patchClamp techniques, using the "cell-attached" mode, the "inside-out" mode, the "outside-out" mode, the "perforated cell" mode, the "one or two electrode" mode, or the "whole cell" mode (*see, e.g.*, Ackerman *et al.*, *New Engl. J. Med.* **336**: 1575-1595 (1997)). Whole cell currents are conveniently determined using the standard methodology (*see, e.g.*, Hamil *et al.*, *Pflugers. Archiv.* **391**: 85 (1981)). Other known assays include: radiolabeled rubidium flux assays and fluorescence assays

using voltage-sensitive dyes (*see, e.g., Vestergaard-Bogind et al., J. Membrane Biol.* **88**: 67-75 (1988); Daniel *et al., J. Pharmacol. Meth.* **25**: 185-193 (1991); Holevinsky *et al., J. Membrane Biology* **137**: 59-70 (1994)). Assays for modulators capable of inhibiting or increasing potassium flow through the channel proteins can be performed by application of the modulators to a bath solution in contact with and comprising cells having a channel of the present invention (*see, e.g., Blatz et al., Nature* **323**: 718-720 (1986); Park, *J. Physiol.* **481**: 555-570 (1994)). Generally, the modulators to be tested are present in the range from about 1 pM to about 100 mM, preferably from about 1 pM to about 1 μ M.

[0135] The effects of the test modulators upon the function of the channels can be measured by changes in the electrical currents or ionic flow or by the consequences of changes in currents and flow. Changes in electrical current or ionic flow are measured by either increases or decreases in flow of ions such as potassium or rubidium ions. The cations can be measured in a variety of standard ways. They can be measured directly by concentration changes of the ions or indirectly by membrane potential or by radio-labeling of the ions. Consequences of the test modulator on ion flow can be quite varied. Accordingly, any suitable physiological change can be used to assess the influence of a test modulator on the channels of this invention. The effects of a test modulator can be measured by a toxin-binding assay. When the functional consequences are determined using intact cells or animals, one can also measure a variety of effects such as transmitter release (*e.g., dopamine*), hormone release (*e.g., insulin*), transcriptional changes to both known and uncharacterized genetic markers (*e.g., northern blots*), cell volume changes (*e.g., in red blood cells*), immunoresponses (*e.g., T cell activation*), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as calcium, or cyclic nucleotides.

IV. Pharmaceutical Compositions For Use as Potassium Ion Channel Modulators

[0136] In another aspect, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a modulator of the present invention (*e.g. a compound of the present invention or a complex of the present invention*).

Formulation of the Modulators

[0137] The modulators of the present invention can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Thus, the modulators of the present invention can be administered by injection, that is, intravenously, intramuscularly,

intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the modulators described herein can be administered by inhalation, for example, intranasally. Additionally, the modulators of the present invention can be administered transdermally. Accordingly, the present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and either a modulator, or a pharmaceutically acceptable salt of a modulator.

[0138] For preparing pharmaceutical compositions from the modulators of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0139] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0140] The powders and tablets preferably contain from 5% or 10% to 70% of the active modulator. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active modulator with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0141] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0142] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0143] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents

as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0144] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0145] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0146] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 10 mg to 500 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

V. Methods for Decreasing Ion Flow in Potassium Ion Channels

[0147] In yet another aspect, the present invention provides a method for decreasing ion flow through potassium ion channels in a cell, comprising contacting the cell with a potassium ion channel modulating amount of a modulator of the present invention.

[0148] In an exemplary embodiment, the potassium ion channels comprise at least one SK subunit.

[0149] The methods provided in this aspect of the invention are useful in the therapy of conditions mediated through potassium ion flow, as well as for the diagnosis of conditions that can be treated by decreasing ion flow through potassium ion channels. Additionally the methods are useful for determining if a patient will be responsive to therapeutic agents which act by modulating potassium ion channels. In particular, a patient's cell sample can be obtained and contacted with a potassium ion channel modulator described above and the ion flow can be measured relative to a cell's ion flow in the absence of the modulator. A

decrease in ion flow will typically indicate that the patient will be responsive to a therapeutic regiment of the modulator.

VI. Methods for Treating Conditions Mediated by Potassium Ion Channels

[0150] In still another aspect, the present invention provides a method for treating a disease through the modulation of potassium ion flow through potassium ion channels. The modulation may be activation or inhibition of the potassium ion flow. Thus, the modulators of the present invention may be inhibitors of potassium ion flow through potassium ion channels (i.e. decrease the flow relative to the absence of the modulator) or activators of potassium ion flow through potassium ion channels (i.e. increase the flow relative to the absence of the modulator).

[0151] The modulators are useful in the treatment of central or peripheral nervous system disorders (*e.g.*, migraine, ataxia, Parkinson's disease, bipolar disorders, trigeminal neuralgia, spasticity, mood disorders, brain tumors, psychotic disorders, myokymia, seizures, epilepsy, hearing and vision loss, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, age-related memory loss, learning deficiencies, anxiety, traumatic brain injury, dysmenorrhea, narcolepsy and motor neuron diseases), and as neuroprotective agents (*e.g.*, to prevent stroke and the like). The modulators of the invention are also useful in treating disease states such as gastroesophageal reflux disorder and gastrointestinal hypomotility disorders, irritable bowel syndrome, secretory diarrhea, asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, ischemia, cerebral ischemia, ischemic heart disease, angina pectoris, coronary heart disease, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, arrhythmia, hypertension, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labor, baldness, cancer, and immune suppression. This method involves administering, to a patient, an effective amount (*e.g.* a therapeutically effective amount) of a modulator of the present invention (a compound or complex of the present invention).

[0152] Thus, the present invention provides a method of decreasing ion flow through potassium ion channels in a cell. The method includes contacting the cell with a potassium ion channel-modulating amount of a modulator of the present invention. In some

embodiments, the potassium ion channel includes at least one SK subunit. The cell may be isolated or form part of an organ or organism.

[0153] The modulators provided herein find therapeutic utility via modulation of potassium ion channels in the treatment of diseases or conditions. The potassium ion channels that are typically modulated are described herein. As noted above, these channels may include homomultimers and heteromultimers.

[0154] In therapeutic use for the treatment of neurological conditions, the modulators utilized in the pharmaceutical method of the invention are administered at the initial dosage of about 0.001 mg/kg to about 1000 mg/kg daily. A daily dose range of about 0.1 mg/kg to about 100 mg/kg is more typical. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the modulator being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the modulator. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day.

[0155] The materials and methods of the present invention are further illustrated by the examples which follow. These examples are offered to illustrate, but not to limit, the claimed invention.

EXAMPLES

General

[0156] In the examples below, unless otherwise stated, temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, "rt," or "RT," (typically a range of from about 18-25 °C); evaporation of solvent was carried out using a rotary evaporator under reduced pressure (typically, 4.5-30 mm Hg) with a bath temperature of up to 60 °C; the course of reactions was typically followed by thin layer chromatography (TLC) and reaction times are provided for illustration only; melting points are uncorrected; products exhibited satisfactory ¹H-NMR and/or microanalytical data; yields are provided for illustration only; and the following conventional abbreviations are also used: mp (melting point), L (liter(s)), mL (milliliters), mmol (millimoles), g (grams), mg (milligrams), min (minutes), and h (hours).

[0157] Unless otherwise specified, all solvents (HPLC grade) and reagents were purchased from suppliers and used without further purification. Reactions were conducted under a blanket of argon unless otherwise stated. Analytical TLC was performed on Whatman Inc. 60 silica gel plates (0.25 mm thickness). Compounds were visualized under UV lamp (254 nm) or by developing with KMnO₄/KOH, ninhydrin or Hanessian's solution. Flash chromatography was done using silica gel from Selectro Scientific (particle size 32-63). ¹H NMR, ¹⁹F NMR and ¹³C NMR spectra were recorded on a Varian 300 machine at 300 MHz, 282 MHz and 75.7 MHz, respectively. Melting points were recorded on a Electrothermal IA9100 apparatus and were uncorrected.

EXAMPLE 1

Preparation of 2 from 1

1.1 Nucleophilic Replacement

[0158] A mixture of 14.7 mmol of **1** and 75 mmol of benzylamine was heated at 220°C for 6 h in a sealed tube. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel to give 7.0 mmol of *N*-benzyl pyridine-2-amine.

[0159] A solution of 6.9 mmol of *N*-benzyl pyridin-2-amine in 15 mL of conc. H₂SO₄ was stirred at 80 °C for 1 h. The reaction mixture was poured into crushed ice and neutralized with 28% NH₄OH. The mixture was extracted with AcOEt and the organic phase was washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 5.0 mmol of **2**.

1.2 Results

[0160] Analytical data for exemplary compounds of structure **2** are provided below.

1.2.a 5-Hexylpyridin-2-ylamine

[0161] ¹H NMR (300 MHz, CDCl₃) δ 7.88 (d, J = 2.2 Hz, 1H), 7.26 (dd, J₁ = 8.4 Hz, J₂ = 2.2 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 4.27 (br s, 2H), 2.45 (d, J = 6.6 Hz, 1H), 1.48-1.56 (m, 2H), 1.27-1.35 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H); MS *m/z*: 178 (M+1).

1.2.b 5-tert-Butylpyridin-2-ylamine

[0162] ¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, J = 2.6 Hz, 1H), 7.47 (dd, J₁ = 8.6 Hz, J₂ = 2.6 Hz, 1H), 6.47 (dd, J₁ = 8.6 Hz, J₂ = 0.7 Hz, 1H), 1.28 (s, 9H); MS *m/z*: 151 (M+1).

1.2.c 5-[2-(Benzyloxy)ethyl]pyridin-2-ylamine

[0163] ^1H NMR (300 MHz, CDCl_3) δ 7.94 (d, $J = 1.8$ Hz, 1H), 7.25–7.37 (m, 6H), 6.45 (dd, $J_1 = 8.4$ Hz, $J_2 = 0.7$ Hz, 1H), 4.51 (s, 2H), 4.31 (br s, 2H), 3.62 (t, $J = 6.9$ Hz, 2H), 2.78 (t, $J = 6.9$ Hz, 2H); MS m/z : 228 ($M+1$).

1.2.d 1-(6-Aminopyridin-3-yl)-4-methylpiperazin-2-one

[0164] ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.80 (d, $J = 2.4$ Hz, 1H), 7.28 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.7$ Hz, 1H), 6.43 (d, $J = 8.8$ Hz, 1H), 5.97 (br s, 2H), 3.53 (t, $J = 5.4$ Hz, 2H), 3.06 (s, 2H), 2.68 (t, $J = 5.4$ Hz, 2H), 2.26 (s, 3H); MS m/z : 279 ($M + 1$).

EXAMPLE 2***Preparation of 2 from 3****2.1 Catalytic Reduction*

[0165] A solution or a suspension of 15 mmol of **3** and 0.5 g of Pd/C (10%) in 150 mL of methanol was stirred overnight under H_2 (1 atm). After filtering through celite, the solution was concentrated under a reduced pressure to give 15 mmol of **2**.

EXAMPLE 3***Preparation of 2****3.1 Iodination of 4*

[0166] A mixture of 240 mmol of **4**, 58 mmol of HIO_4 , and 240 mmol of I_2 in 60 mL of water, 4 mL of concentrated H_2SO_4 , and 200 mL of acetic acid was stirred at 80 °C for 4 h. Excess I_2 was neutralized by the addition of 200 mL of saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution. The resulting aqueous solution was extracted with EtOAc. The organic phase was washed with saturated NaCl, dried over MgSO_4 , and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel to give 136 mmol of **5**.

3.2 Suzuki Cross Coupling

[0167] A mixture of 15 mmol of **5**, 15 mmol of **6**, 0.35 mmol of $\text{Pd}_2(\text{dba})_3$, and 2.4 mmol of PPh_3 in 40 mL of toluene, 20 mL of ethanol, and 20 mL of water was refluxed overnight under N_2 . The reaction mixture was diluted with 300 mL of ethyl acetate and the organic solution was washed with saturated NaCl, dried over MgSO_4 , and concentrated under a

reduced pressure. The residue was purified by column chromatography on silica gel to give 13.1 mmol of **2**.

3.3 Results

[0168] Analytical data for exemplary compounds of structure **2** are provided below.

3.3.a 5-(2-Methoxy-phenyl)-pyridin-2-ylamine

[0169] ^1H NMR (300 MHz, DMSO- d_6) δ 7.99 (d, J = 2.0 Hz, 1H), 7.48 (dd, J_1 = 8.6 Hz, J_2 = 2.3 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 6.1 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.96 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 8.5 Hz, 1H), 5.94 (s, 2H), 3.73 (s, 3H); MS m/z : 201 ($M + 1$).

3.3.b (5-Methyl-furan-2-yl)-pyridin-2-ylamine

[0170] ^1H NMR (300 MHz, DMSO- d_6) δ 8.17 (d, J = 2.0 Hz, 1H), 7.63-7.52 (m, 2H), 6.48 (d, J = 3.2 Hz, 1H), 6.43 (d, J = 8.7 Hz, 1H), 6.08 (s, 2H), 2.27 (s, 3H); MS m/z : 175 ($M + 1$).

3.3.c [3,3']Bipyridinyl-6-ylamine

[0171] ^1H NMR (300 MHz, DMSO- d_6) δ 8.78 (d, J = 2.1 Hz, 1H), 8.44 (dd, J_1 = 4.9 Hz, J_2 = 1.6 Hz, 1H), 8.27 (d, J = 2.2 Hz, 1H), 7.94 (dt, J_1 = 8.0 Hz, J_2 = 1.9 Hz, 1H), 7.73 (dd, J_1 = 8.7 Hz, J_2 = 2.6 Hz, 1H), 7.38 (dd, J_1 = 8.7 Hz, J_2 = 2.6 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 6.17 (s, 2H); MS m/z : 172 ($M + 1$).

3.3.d 5-(4-Fluoro-phenyl)-4-methyl-pyridin-2-ylamine

[0172] ^1H NMR (300 MHz, DMSO- d_6) δ 7.68 (s, 1H), 7.30 (dd, J_1 = 8.5 Hz, J_2 = 5.7 Hz, 2H), 7.19 (t, J = 8.9 Hz, 2H), 6.33 (s, 1H), 5.87 (s, 2H), 2.07 (s, 3H); MS m/z : 203 ($M + 1$).

3.3.e 5-(3-Fluoro-phenyl)-pyridin-2-ylamine

[0173] ^1H NMR (300 MHz, DMSO- d_6) δ 8.27 (d, J = 2.3 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.42-7.38 (m, 3H), 7.08-7.01 (m, 1H), 6.49 (d, J = 8.6 Hz, 1H), 6.15 (s, 2H); MS m/z : 189 ($M + 1$).

3.3.f 5-Thiophen-2-yl-pyridin-2-ylamine

[0174] ^1H NMR (300 MHz, DMSO- d_6) δ 8.19 (d, J = 2.3 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 5.1 Hz, 1H), 7.25 (d, J = 3.3 Hz, 1H), 7.04 (t, J = 4.7 Hz, 1H), 6.45 (d, J = 8.7 Hz, 1H), 6.14 (s, 2H); MS m/z : 177 ($M + 1$).

EXAMPLE 4***Preparation of 8 from 5******4.1 Ullmann Cross-Coupling***

[0175] To a solution of 50.0 mmol of **5** and 60.0 mmol of **7** in 50.0 mL of 1,4-dioxane was added 0.500 mmol of copper (I) iodide followed by the addition of 100 mmol of K₃PO₄ and 5 mmol of *trans*-cyclohexanediamine, then the resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled to rt and diluted with 500 mL of H₂O. The resulting aqueous solution was extracted with CHCl₃. The organic phase was washed with saturated NaCl, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography to give 43.4 mmol of **8**.

4.2 Results

[0176] Analytical data for exemplary compounds of structure **8** are provided below.

4.2.a tert-Butyl 4-(6-aminopyridin-3-yl)-3-oxopiperazine-1-carboxylate

[0177] ¹H NMR (400 MHz, CDCl₃) δ 7.97-8.00 (m, 1H), 7.35-7.40 (m, 1H), 6.50-6.54 (m, 1H), 4.54 (br s, 2H), 4.24 (s, 2H), 3.65-3.69 (m, 2H), 3.75-3.80 (m, 2H), 1.50 (s, 9H); MS *m/z*: 293 (M+1).

4.2.b 5-(4-Methyl-1,4-diazepan-1-yl)pyridin-2-ylamine

[0178] ¹H NMR (400 MHz, DMSO-d₆) δ 7.46 (d, J = 3.5 Hz, 1H), 6.95 (dd, J₁ = 8.8 Hz, J₂ = 3.5 Hz, 1H), 6.38 (d, J = 8.8 Hz, 1H), 5.04 (br s, 2H), 3.26-3.40 (m, 4H), 2.53-2.59 (m, 2H), 2.41-2.47 (m, 2H), 2.24 (s, 3H), 1.78-1.90 (m, 2H); MS *m/z*: 207 (M+1).

4.2.c 4-(6-Aminopyridin-3-yl)-1-methyl-1,4-diazepan-5-one

[0179] ¹H NMR (400 MHz, DMSO-d₆) δ 7.71 (d, J = 2.9 Hz, 1H), 7.18 (dd, J₁ = 8.8 Hz, J₂ = 2.9 Hz, 1H), 6.41 (d, J = 8.8 Hz, 1H), 5.90 (br s, 2H), 3.64-3.71 (m, 2H), 2.51-2.62 (m, 4H), 2.26 (s, 3H); MS *m/z*: 221 (M+1).

4.2.d tert-Butyl 4-(6-aminopyridin-3-yl)-5-oxo-1,4-diazepan-1-carboxylate

[0180] ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 2.8 Hz, 1H), 7.29 (dd, J₁ = 8.8 Hz, J₂ = 2.8 Hz, 1H), 6.50 (d, J = 8.8 Hz, 1H), 4.54 (br s, 2H), 3.71-3.75 (m, 6H), 2.80-2.83 (m, 2H), 1.49 (s, 9H); MS *m/z*: 307 (M+1).

EXAMPLE 5

Preparation of 8

5.1 Buchwald Cross-Coupling

[0181] A mixture of 30 mmol of **9**, 30 mmol of **7**, 0.04 mmol of Pd₂(dba)₃, 0.08 mmol of *rac*-2,2'-bis(phenylphosphino)-1,1'-binaphthyl (BINAP), and 42 mmol of Cs₂CO₃ in 100 mL of dry toluene was stirred at 80 °C for two days under N₂. The reaction mixture was diluted with 400 mL of ethyl acetate and the organic solution was washed with saturated NaCl, dried over MgSO₄, and concentrated under reduced pressure. The residue was crystallized in ethyl acetate to yield 15.8 mmol of **10**.

[0182] A solution or a suspension of 15 mmol of **10** and 0.5 g of Pd/C (10%) in 150 mL of methanol was stirred overnight under H₂ (1 atm). After filtering through celite, the solution was concentrated under a reduced pressure to give 15 mmol of **8**.

5.2 Results

[0183] Analytical data for exemplary compounds of structure **8** are provided below.

5.2.a 5-(4-Methyl-piperazin-1-yl)-pyridin-2-ylamine

[0184] ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.56 (d, J = 2.7 Hz, 1H), 7.13 (dd, J₁ = 8.9 Hz, J₂ = 2.9 Hz, 1H), 6.36 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 2.89 (t, J = 5.0 Hz, 4H), 2.40 (t, J = 5.0 Hz, 4H), 2.18 (s, 3H); MS *m/z*: 193 (M + 1).

5.2.b 4-Methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-ylamine

[0185] ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.56 (d, J = 2.8 Hz, 1H), 7.11 (dd, J₁ = 8.9 Hz, J₂ = 3.0 Hz, 1H), 6.35 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 3.26 (d, J = 12.0 Hz, 2H), 2.45 (dt, J₁ = 9.3 Hz, J₂ = 4.2 Hz, 2H), 1.64 (d, J = 12.5 Hz, 2H), 1.4-1.3 (m, 1H), 1.44-1.28 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H); MS *m/z*: 192 (M + 1).

5.2.c 1-(6-Aminopyridin-3-yl)-pyrrolidin-2-one

[0186] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.03 (d, J = 2.6 Hz, 1H), 7.63 (dd, J₁ = 8.9 Hz, J₂ = 2.6 Hz, 1H), 6.42 (d, J = 8.9 Hz, 1H), 5.83 (s, 2H), 3.70 (t, J = 7.0 Hz, 2H), 2.39 (t, J₁ = 7.8 Hz, 2H), 2.01 (dd, J₁ = 7.1 Hz, J₂ = 7.9 Hz, 2H); MS *m/z*: 178 (M + 1).

5.2.d 1-(6-Aminopyridin-3-yl)piperidin-2-one

[0187] ^1H NMR (400 MHz, DMSO- d_6) δ 7.76 (d, J = 2.4 Hz, 1H), 7.24 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.42 (d, J = 8.8 Hz, 1H), 5.90 (br s, 2H), 3.49 (t, J = 6.0 Hz, 2H), 2.34 (t, J = 6.0 Hz, 2H), 1.77-1.85 (m, 4H); MS m/z : 192 ($M + 1$).

5.2.e 1-(6-Aminopyridin-3-yl)piperidin-4-ol

[0188] ^1H NMR (400 MHz, DMSO- d_6) δ 7.59 (d, J = 2.4 Hz, 1H), 7.14 (dd, J_1 = 9.2 Hz, J_2 = 2.4 Hz, 2H), 6.38 (d, J = 9.2 Hz, 1H), 5.34 (br s, 2H), 4.63 (1H, d, J = 4.4 Hz), 3.50-3.57 (m, 1H), 3.18-3.23 (m, 2H), 2.59-2.65 (m, 2H), 1.76-1.83 (m, 2H), 1.44-1.54 (m, 2H); MS m/z : 194 ($M + 1$).

5.2.f 5-Piperidin-1-ylpyridin-2-ylamine

[0189] ^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, J = 2.8 Hz, 1H), 7.17 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 6.47 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 4.11 (br s, 2H), 2.98 (d, J = 5.2 Hz, 2H), 2.97 (d, J = 5.2 Hz, 2H), 1.68-1.74 (m, 4H), 1.51-1.57 (m, 2H); MS m/z : 178 ($M + 1$).

5.2.g 5-(4-Isopropylpiperazin-1-yl)pyridin-2-ylamine

[0190] ^1H NMR (300 MHz, DMSO- d_6) δ 7.55-7.60 (m, 1H), 7.10-7.17 (m, 1H), 6.35-6.42 (m, 1H), 5.34 (br s, 2H), 2.85-2.94 (m, 4H), 2.50-2.70 (m, 5H), 0.95-1.02 (m, 6H); MS m/z : 221 ($M + 1$).

5.2.h tert-Butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate

[0191] ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 2.8 Hz, 1H), 7.17 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 4.21 (br s, 2H), 3.57 (t, J = 5.2 Hz, 4H), 2.96 (t, J = 5.2 Hz, 4H), 1.48 (s, 9H); MS m/z : 279 ($M + 1$).

5.2.i 1-(6-Aminopyridin-3-yl)-4-methylpiperazin-2-one

[0192] ^1H NMR (300 MHz, DMSO- d_6) δ 7.80 (d, J = 2.4 Hz, 1H), 7.28 (dd, J_1 = 8.7 Hz, J_2 = 2.7 Hz, 1H), 6.43 (d, J = 8.8 Hz, 1H), 5.97 (br s, 2H), 3.53 (t, J = 5.4 Hz, 2H), 3.06 (s, 2H), 2.68 (t, J = 5.4 Hz, 2H), 2.26 (s, 3H); MS m/z : 207 ($M + 1$).

5.2.j 5-[3-(Dimethylamino)pyrrolidin-1-yl]pyridin-2-ylamine

[0193] ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 2.8 Hz, 1H), 6.83 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 3.96 (br s, 2H), 3.24-3.41 (m, 3H), 3.09 (t, J = 8.0 Hz, 1H), 2.82-2.90 (m, 1H), 2.35 (s, 6H), 2.14-2.22 (m, 1H), 1.86-1.96 (m, 1H); MS m/z : 206 ($M + 1$).

5.2.k *N⁵-1-Azabicyclo[2.2.2]oct-3-ylpyridin-2,5-yldiamine*

[0194] ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 2.8 Hz, 1H), 6.86 (dd, J₁ = 8.4 Hz, J₂ = 2.8 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 4.00 (br s, 2H), 3.34-3.37 (m, 1H), 2.80-2.90 (m, 4H), 2.50-2.53 (m, 1H), 1.23-1.97 (m, 6H); MS *m/z*: 218 (M + 1).

5.2.l *5-(2,4,5-Trimethylpiperazin-1-yl)pyridin-2-ylamine*

[0195] ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 2.8 Hz, 1H), 7.30 (dd, J₁ = 8.8 Hz, J₂ = 2.8 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 4.29 (br s, 2H), 3.06 (m, 1H), 2.86 (dd, J₁ = 11.2 Hz, J₂ = 3.2 Hz, 2H), 2.66 (m, 1H), 2.33 (m, 4H), 2.12 (t, J = 10.8 Hz, 1H), 1.07 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H); MS *m/z*: 221 (M + 1).

5.2.m *N⁵-Methyl-N⁵-(1-methylpyrrolidin-3-yl)pyridin-2,5-yldiamine*

[0196] ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 2.8 Hz, 1H), 7.16 (dd, J₁ = 8.8 Hz, J₂ = 2.8 Hz, 1H), 6.47 (d, J = 8.8 Hz, 1H), 4.12 (br s, 2H), 3.97-4.04 (m, 1H), 2.72 (s, 3H), 2.60-2.70 (m, 2H), 2.50-2.56 (m, 2H), 2.34 (s, 3H), 2.04-2.10 (m, 1H), 1.77-1.83 (m, 1H); MS *m/z*: 207 (M + 1).

5.2.n *5-(3-Methylpiperazin-1-yl)pyridin-2-ylamine*

[0197] ¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, J = 2.8 Hz, 1H), 7.15 (dd, J₁ = 8.8 Hz, J₂ = 2.8 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.33 (m, 1H), 4.21 (br s, 2H), 3.92-3.96 (m, 1H), 3.19-3.26 (m, 2H), 3.08-3.11 (m, 1H), 2.82 (dd, J₁ = 11.6 Hz, J₂ = 4.0 Hz, 1H), 2.61-2.68 (m, 1H), 1.48 (s, 9H), 1.32 (d, J = 6.8 Hz, 3H); MS *m/z*: 293 (M + 1).

5.2.o *5-(3,5-Dimethylpiperazin-1-yl)pyridin-2-ylamine*

[0198] ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 2.8 Hz, 1H), 7.16 (dd, J₁ = 8.8 Hz, J₂ = 2.8 Hz, 1H), 6.50 (d, J = 8.8 Hz, 1H), 4.18-4.24 (m, 2H), 3.08-3.11 (m, 2H), 2.80 (dd, J₁ = 11.6 Hz, J₂ = 4.0 Hz, 1H), 1.49 (s, 9H), 1.37 (d, J = 6.8 Hz, 6H); MS *m/z*: 307 (M+1).

5.2.p *N⁵-(2-Methoxyethyl)-N⁵-methylpyridin-2,5-yldiamine*

[0199] MS *m/z*: 182 (M+1).

5.2.q *5-(4-Methoxypiperidin-1-yl)pyridin-2-ylamine*

[0200] MS *m/z*: 208 (M+1).

EXAMPLE 6

Preparation of 8

6.1 Ullmann Cross-Coupling

[0201] To a solution of 24.6 mmol of **9** and 27.3 mmol of **7** in 50 mL of 1,4-dioxane was added 4.92 mmol of copper (I) iodide followed by the addition of 49.2 mmol of K₃PO₄ and 4.92 mmol of *trans*-cyclohexanediamine, then the resulting mixture was stirred at 100°C for 12 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*.

The residue was diluted with CHCl₃, poured into water, and insoluble material was removed by celite filtration. The filtrate was extracted with CHCl₃, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography to give 7.87 mmol of nitro derivative.

[0202] A solution of 7.66 mmol of nitro derivative and 0.5 g of Pd/C (10%) in 150 mL of methanol was stirred overnight under H₂ (1 atm). After filtering through celite, the solution was concentrated under reduced pressure to give 4.75 mmol of **8**.

6.2 Results

[0203] Analytical data for exemplary compound of structure **8** are provided below.

6.2.a 4-(6-Aminopyridin-3-yl)-1-benzyl-1,4-diazepan-5-one

[0204] ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70 (d, J = 2.4 Hz, 1H), 7.17 (dd, J₁ = 8.8 Hz, J₂ = 2.4 Hz, 1H), 7.30-7.36 (m, 5H), 6.40 (d, J = 8.8 Hz, 1H), 5.90 (br s, 2H), 3.66-3.72 (m, 2H), 3.59 (br s, 2H), 2.59-2.71 (m, 6H); MS *m/z*: 327 (M+1).

EXAMPLE 7

Preparation of 12

7.1 Halogenation

[0205] To a solution of 30.7 mmol of **11** and 5 mL of bromine in 48 mL of hydrobromic acid (48%) at 0 °C was added 24 mL (25 M) of aqueous NaNO₂. The mixture was stirred for 1 h at rt before it was neutralized by 145 mL of 3M NaOH. The aqueous solution was extracted with ethyl acetate, and the organic phase was washed with saturated NaCl, dried over MgSO₄, and concentrated under a reduced pressure. The crude product was purified by column chromatography to give 24.6 mmol of **12**.

7.2 Results

[0206] Analytical data for exemplary compounds of structure **12** are provided below.

7.2.a 2-Bromo-5-chloro-pyridine

[0207] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (d, *J* = 2.8 Hz, 1H), 7.89 (dd, *J*₁ = 8.5 Hz, *J*₂ = 2.7 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H); MS *m/z*: 192 (*M* + 1).

7.2.b 2-Bromo-5-(4-fluoro-phenyl)-pyridine

[0208] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.68 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J*₁ = 8.3 Hz, *J*₂ = 2.6 Hz, 1H), 7.80-7.70 (m, 3H), 7.34 (d, *J* = 6.6 Hz, 1H), 7.32 (d, *J* = 6.8 Hz, 1H); MS *m/z*: 252 (*M* + 1).

EXAMPLE 8

Preparation of 14

8.1 Stannylation

[0209] To a solution of 17.4 mmol of **13** in 60 mL of dry THF at -78 °C under N₂ was added 19.2 mmol of *n*-BuLi (2.5 M in hexane), and the resulting brown solution was stirred for 30 min before 20.9 mmol of Bu₃SnCl was added. The reaction mixture was allowed to warm to room temperature overnight. After the reaction was quenched with saturated NH₄Cl and the mixture was extracted with ethyl acetate, the combined organic phase was washed with saturated NaCl, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give 10.5 mmol of **14**.

8.2 Results

[0210] Analytical data for exemplary compounds of structure **14** are provided below.

8.2.a 4-Methyl-2-tributylstannanyl-pyridine

[0211] ¹H NMR (300 MHz, CDCl₃) δ 8.57 (d, *J* = 5.0 Hz, 1H), 7.21 (s, 1H), 6.93 (d, *J* = 4.7 Hz, 1H), 2.29 (s, 3H), 1.61-1.47 (m, 6H), 1.39-1.29 (m, 6H), 1.16-1.08 (m, 6H), 0.87 (t, *J* = 7.3 Hz, 9H); MS *m/z*: 384 (*M* + 1).

8.2.b 2-Methoxy-6-tributylstannanyl-pyridine

[0212] ¹H NMR (300 MHz, CDCl₃) δ 7.39 (dd, J₁ = 8.3 Hz, J₂ = 6.9 Hz, 1H), 6.98 (d, J = 6.1 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 1.62-1.53 (m, 6H), 1.38-1.27 (m, 6H), 1.12-1.05 (m, 6H), 0.89 (t, J = 5.9 Hz, 9H); MS *m/z*: 400 (M + 1).

8.2.c 5-Methyl-2-tributylstannanyl-pyridine

[0213] ¹H NMR (300 MHz, CDCl₃) δ 8.56 (s, 1H), 7.30-7.24 (m, 2H), 2.25 (s, 3H), 1.58-1.44 (m, 6H), 1.36-1.25 (m, 6H), 1.11-1.04 (m, 6H), 0.86 (t, J = 7.1 Hz, 9H); MS *m/z*: 384 (M + 1).

8.2.d 4-Pyrrolidin-1-yl-2-tributylstannanyl-pyridine

[0214] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.14 (d, J = 4.5 Hz, 1H), 6.68-6.64 (m, 1H), 6.59 (d, J = 2.4 Hz, 1H), 3.41 to 3.39 (m, 4H), 1.97 (bs, 4H), 1.58-1.41 (m, 6H), 1.38-1.22 (m, 6H), 1.20-1.00 (m, 6H), 0.83 (t, J = 7.3 Hz, 9H); MS *m/z*: 439 (M + 1).

EXAMPLE 9***Preparation of 16****9.1 General Method: Stille Cross-Coupling*

[0215] A mixture of 0.3 mmol of **15**, 0.36 mmol of **14**, and 0.015 mmol of Pd(PPh₃)₄ in 4 mL of dry toluene was stirred for 2 days at 70 °C under N₂. The reaction was quenched with 10 mL of saturated NH₄Cl. After the mixture was extracted with EtOAc, the organic phase was washed with saturated NaCl, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give 0.063 mmol of **16**.

9.2 Results

[0216] Analytical data for an exemplary compound of structure **16** is provided below.

9.2.a 2-Chloro-4-pyridin-2-yl-pyrimidine

[0217] ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.79 (d, J = 5.0 Hz, 1H), 8.73 (d, J = 3.8 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.03-7.97 (m, 1H), 7.58-7.53 (m, 1H); MS *m/z*: 192 (M + 1).

EXAMPLE 10***Preparation of 16****10.1 General Method: Nucleophilic Addition and Oxidation*

[0218] To a solution of 127 mmol of **14** in 400 mL of dry THF at -78 °C was added 139 mmol of *n*-butyllithium (2.5 M in hexane) and the solution was stirred for 30 min before 139 mmol of **17** in 100 mL of dry THF was added over a period of 10 min. The resulting mixture was allowed to warm to room temperature with stirring overnight. The reaction was quenched with 10 mL of acetic acid. To the acidic mixture was added 139 mmol of DDQ and the resulting mixture was stirred for 2 days at room temperature before it was quenched with saturated NaHCO₃. After the mixture was extracted with ethyl acetate, the organic phase was washed with saturated NaCl, dried over MgSO₄, and concentrated *in vacuo* to afford 62 mmol of **16**.

EXAMPLE 11***Preparation of 18****11.1 General Method*

[0219] To a solution of 1.34 mmol of **2** or **8** in 20 mL of anhydrous THF was added 2.68 mmol of NaH (60% in mineral oil) and the solution was stirred for 10 min before the addition of 1.34 mmol of **15**. The resulting mixture was stirred at reflux for 1 day under N₂ and the reaction was quenched with saturated NH₄Cl. The reaction mixture was diluted with 100 mL of ethyl acetate and the organic solution was washed with saturated NaCl, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to afford 0.48 mmol of **18**.

11.2 Results

[0220] Analytical data for exemplary compounds of structure **18** are provided below.

11.2.a (2-Chloro-pyrimidin-4-yl)-pyridin-2-yl-amine

[0221] ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 8.32 (d, *J* = 6.0 Hz, 2H), 7.83 (d, *J* = 5.5 Hz, 1H), 7.81-7.74 (m, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.07-7.02 (m, 1H); MS *m/z*: 207 (*M* + 1).

11.2.b (5-Chloro-pyridin-2-yl)-(2-chloro-pyrimidin-4-yl)-amine

[0222] ^1H NMR (300 MHz, DMSO- d_6) δ 10.83 (s, 1H), 8.35 (d, J = 5.8 Hz, 2H), 7.90 (dd, J_1 = 2.8 Hz, J_2 = 8.9 Hz, 1H), 7.71 (d, J = 5.7 Hz, 1H), 7.60 (d, J = 9.1 Hz, 1H); MS m/z : 241 ($M + 1$).

EXAMPLE 12***Preparation of 19****12.1 General Method: Nucleophilic Replacement*

[0223] To a solution of 0.58 mmol of **2** or **8** in 20 mL of anhydrous THF was added 1.05 mmol of NaH (60% in mineral oil) and the solution was stirred for 10 min before the addition of 0.53 mmol of **16**. The resulting mixture was stirred at reflux for 16 h under N_2 and then the reaction was quenched with saturated NH_4Cl . The reaction mixture was diluted with 100 mL of ethyl acetate and the organic solution was washed with saturated NaCl, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to afford a quantitative yield of **19**.

12.2 Results

[0224] Analytical data for exemplary compounds of structure **19** are provided below.

12.2.a (5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-pyridin-2-yl-amine

[0225] ^1H NMR (300 MHz, DMSO- d_6) δ 10.75 (bs, 1H), 8.90 (d, J = 5.2 Hz, 1H), 8.59-8.48 (m, 3H), 8.40 (t, J = 7.8 Hz, 1H), 8.26-8.12 (m, 2H), 7.90 (t, J = 6.4 Hz, 1H), 7.44-7.39 (m, 1H), 4.12 (s, 3H); MS m/z : 280 ($M + 1$).

12.2.b (5-Chloro-pyridin-2-yl)-(5-methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-amine · 2HCl

[0226] ^1H NMR (300 MHz, DMSO- d_6) δ 10.10 (s, 1H), 8.86 (d, J = 4.7 Hz, 1H), 8.52-8.32 (m, 4H), 8.26 (d, J = 8.9 Hz, 1H), 8.06 (dd, J_1 = 8.9 Hz, J_2 = 2.5 Hz, 1H), 7.92-7.87 (m, 1H), 4.09 (s, 3H); MS m/z : 314 ($M + 1$).

12.2.c (5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(5-pyrrolidin-1-yl-pyridin-2-yl)-amine · 2HCl

[0227] ^1H NMR (300 MHz, DMSO- d_6) δ 10.85 (bs, 1H), 8.89 (d, J = 5.0 Hz, 1H), 8.45 (d, J = 7.8 Hz, 1H), 8.35 (s, 2H), 7.97 (d, J = 9.4 Hz, 1H), 7.91-7.86 (m, 1H), 7.84 (d, J = 3.0

Hz, 1H), 7.55 (dd, $J_1 = 9.3$ Hz, $J_2 = 3.0$ Hz, 1H), 4.11 (s, 3H), 3.37-3.30 (m, 4H), 1.99 (t, $J = 6.4$ Hz, 4H); MS m/z : 349 ($M + 1$).

12.2.d [5-(3-Fluoro-phenyl)-pyridin-2-yl]-(5-methoxy-2-pyridin-2-yl-pyrimidin-4-yl)- amine · 2HCl

[0228] ^1H NMR (300 MHz, DMSO- d_6) δ 10.55 (bs, 1H), 8.93-8.89 (m, 2H), 8.56 (d, $J = 7.9$ Hz, 1H), 8.46-8.41 (m, 3H), 8.34 (d, $J = 8.7$ Hz, 1H), 7.96-7.91 (m, 1H), 7.71-7.63 (m, 2H), 7.59-7.51 (d, 1H), 7.30-7.22 (m, 1H), 4.12 (s, 3H); MS m/z : 374 ($M + 1$).

12.2.e 1-[6-(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-ylamino)-pyridin-3-yl]-pyrrolidin-2-one · 2HCl

[0229] ^1H NMR (300 MHz, DMSO- d_6) δ 10.27 (bs, 1H), 8.86 (d, $J = 4.7$ Hz, 1H), 8.73 (d, $J = 2.7$ Hz, 1H), 8.45 (d, $J = 7.8$ Hz, 1H), 8.40-8.30 (m, 4H), 7.88-7.83 (m, 1H), 4.10 (s, 3H), 3.90 (t, $J = 7.0$ Hz, 2H), 2.55-2.47 (m, 2H), 2.11 (t, $J = 7.5$ Hz, 2H); MS m/z : 363 ($M + 1$).

12.2.f (5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine · 3HCl

[0230] ^1H NMR (300 MHz, DMSO- d_6) δ 10.67 (bs, 1H), 8.88 (d, $J = 4.6$ Hz, 1H), 8.38 (d, $J = 7.8$ Hz, 1H), 8.31-8.26 (m, 3H), 8.01 (d, $J = 9.0$ Hz, 1H), 7.86-7.78 (m, 2H), 4.10 (s, 3H), 3.94 (d, $J = 12.7$ Hz, 2H), 3.50 (d, $J = 11.7$ Hz, 2H), 3.32-3.14 (m, 4H), 2.79 (d, $J = 4.5$ Hz, 3H); MS m/z : 378 ($M + 1$).

12.2.g (5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(4-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-yl)- amine · 2HCl

[0231] ^1H NMR (300 MHz, DMSO- d_6) δ 10.59 (bs, 1H), 8.91 (d, $J = 4.9$ Hz, 1H), 8.58-8.44 (m, 3H), 8.43 (s, 1H), 8.25-8.19 (m, 2H), 8.00-7.94 (m, 1H), 4.11 (s, 3H), 3.71 (d, $J = 11.8$ Hz, 2H), 3.16 (bs, 2H), 1.78 (d, $J = 12.5$ Hz, 2H), 1.70-1.45 (m, 3H), 0.95 (d, $J = 6.1$ Hz, 3H); MS m/z : 377 ($M + 1$).

EXAMPLE 13

Preparation of 20

13.1 Negishi Cross-Coupling

[0232] A mixture of 0.08 mmol of **18**, 0.08 mmol of **14**, and 0.015 mmol of $\text{Pd}(\text{PPh}_3)_4$ in 4 mL of dry THF was stirred at reflux for 2 days under N_2 . The reaction was quenched with 10 mL of saturated NH_4Cl . After the mixture was extracted with EtOAc, the organic phase

was washed with saturated NaCl, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 0.03 mmol of **20**.

13.2 Results

[0233] Analytical data for exemplary compounds of structure **20** are provided below.

13.2.a Pyridin-2-yl-(4-pyridin-2-yl-pyrimidin-2-yl)-amine

[0234] ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.91 (s, 1H), 8.74 (d, J = 3.5 Hz, 1H), 8.69 (d, J = 5.1 Hz, 1H), 8.42 (d, J = 7.8 Hz, 1H), 8.34 (d, J = 8.3 Hz, 1H), 8.30 (d, J = 3.6 Hz, 1H), 8.04 (t, J = 7.8 Hz, 1H), 7.81 (d, J = 4.8 Hz, 2H), 7.59-7.54 (m, 1H), 7.03-6.98 (m, 1H); MS *m/z*: 250 (M + 1).

13.2.b (5-Chloro-pyridin-2-yl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine

[0235] ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.24 (s, 1H), 8.76-8.69 (m, 2H), 8.43-8.32 (m, 2H), 8.03 (dd, J₁ = 7.8 Hz, J₂ = 6.0 Hz, 1H), 7.90 (dd, J₁ = 8.9 Hz, J₂ = 2.5 Hz, 1H), 7.86-7.82 (m, 1H), 7.61-7.54 (m, 2H); MS *m/z*: 284 (M + 1).

13.2.c (5-Phenyl-pyridin-2-yl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine

[0236] ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.12 (s, 1H), 8.76-8.71 (m, 2H), 8.64 (d, J = 2.5 Hz, 1H), 8.45 (d, J = 8.3 Hz, 2H), 8.14 (dd, J₁ = 2.4 Hz, J₂ = 8.7 Hz, 1H), 8.04 (dt, J₁ = 1.8 Hz, J₂ = 7.8 Hz, 1H), 7.82 (d, J = 5.0 Hz, 1H), 7.71 (d, J = 7.3 Hz, 2H), 7.60-7.55 (m, 1H), 7.50-7.44 (m, 2H), 7.37 (d, J = 7.3 Hz, 1H); MS *m/z*: 326 (M + 1).

EXAMPLE 14

Preparation of **23**

14.1 General Method

[0237] A mixture of 20.0 mmol of the corresponding carboxylic acid of **22**, 15 mL of SOCl₂, and 5 drops of DMF was stirred at 60°C for 3 h. The reaction mixture was concentrated *in vacuo*. To a solution of the crude **22** in 50 mL of THF was added 20 mmol of **21** and 60 mmol of Et₃N and stirred at room temperature for 2 h. The reaction mixture was concentrated and the residue was diluted with water and AcOEt. The precipitates were collected by filtration and washed with EtOH to give 1.1 mmol of **23**.

EXAMPLE 15***Preparation of 24****15.1 General Method*

[0238] To a solution of 6.9 mmol of **23** in 20 mL of THF and 20 mL of t-BuOH was added 15 mmol of tBuOK and stirred at 80°C for 2 h. The reaction mixture was quenched with 3 g of NH₄Cl and extracted with AcOEt. The organic phase was washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was washed with AcOEt-n-hexane (1:2) to give 6.1 mmol of **24**.

EXAMPLE 16***Preparation of 25****16.1 General Method*

[0239] A mixture of 5.5 mmol of **24** in 15 mL of POCl₃ was stirred at 120°C for 1 h. The reaction mixture was concentrated *in vacuo* and diluted with AcOEt and H₂O, and quenched with K₂CO₃. The precipitates were collected by filtration to give 4.7 mmol of **25**.

16.2 Results

[0240] Analytical data for exemplary compound of structure **25** is provided below.

16.2.a 4-Chloro-2-pyridin-2-ylquinazoline

[0241] ¹H NMR (400 MHz, CDCl₃) δ 8.79 (d, J = 4.9 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 8.20 (dd, J₁ = 7.8 Hz, J₂ = 1.0 Hz, 1H), 8.11 (dt, J₁ = 7.8 Hz, J₂ = 1.5 Hz, 1H), 7.83-7.92 (m, 2H), 7.68-7.71 (m, 1H), 7.57-7.61 (m, 1H); MS *m/z*: 243 (M + 1).

EXAMPLE 17***Preparation of 26****17.1 General Method*

[0242] To a solution of 1.66 mmol of **25** in 15 mL of DMF was added 5 mmol of 60% NaH in oil at room temperature and 1.66 mmol of **2** or **8**, and the resulting mixture was stirred at 60°C for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was diluted with water and AcOEt. The mixture was extracted with AcOEt and the organic

phase was extracted with diluted HCl. Aqueous phase was made alkaline with K₂CO₃ and extracted with AcOEt, and then organic phase was washed with brine, dried over MgSO₄, and concentrated. The residue was purified by column chromatography on silica gel to give 0.94 mmol of ca. 1:1 tautomeric mixture of **26**.

17.2 General Method

[0243] Analytical data for exemplary compound of structure **26** is provided below.

17.2.a N,2-dipyridin-2-ylquinazolin-4-amine and N-[(4Z)-2-pyridin-2-ylquinazolin-4(3H)-ylidene]pyridin-2-amine (ca. 1:1 tautomeric mixture)

[0244] ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.18 (s, 0.5H), 8.72-8.86 (m, 2H), 8.42-8.57 (m, 2.5H), 8.08 (dt, J₁ = 7.8 Hz, J₂ = 2.0 Hz, 0.5H), 7.47-7.98 (m, 6H), 7.32 (d, J = 8.3 Hz, 0.5H), 7.11-7.17 (m, 1H); MS *m/z*: 300 (M + 1).

EXAMPLE 18

Preparation of **29**

18.1 General Method

[0245] A mixture of 3.0 mmol of **27**, 3.0 mmol of **14**, and 0.09 mmol of Pd(PPh₃)₄ in 20 mL of toluene was stirred at 100°C for 20 h. The reaction mixture was diluted with AcOEt and H₂O, filtrated through celite, and then extracted with AcOEt. The organic phase was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 0.46 mmol of **28**.

18.2 Results

[0246] Analytical data for exemplary compound of structure **28** is provided below.

18.2.a 2-Chloro-4-pyridin-2-ylquinazoline

[0247] ¹H NMR (300 MHz, CDCl₃) δ 8.95-8.99 (m, 1H), 8.83-8.86 (m, 1H), 8.27 (dt, J₁ = 7.9 Hz, J₂ = 0.9 Hz, 1H), 7.92-8.07 (m, 3H), 7.65-7.71 (m, 1H), 7.49-7.54 (m, 1H); MS *m/z*: 243 (M + 1).

18.3 General Method

[0248] To a solution of 1.66 mmol of **28** in 15 mL of DMF was added 5 mmol of 60% NaH in oil at room temperature and 1.66 mmol of **2** or **8**, and the resulting mixture was stirred at 60°C for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was

diluted with water and AcOEt. The mixture was extracted with AcOEt and the organic phase was extracted with diluted HCl. Aqueous phase was made alkaline with K_2CO_3 and extracted with AcOEt, and then organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel to give 0.90 mmol of **29**.

18.4 Results

[0249] Analytical data for exemplary compound of structure **29** is provided below.

18.4.a N,4-Dipyridin-2-ylquinazolin-2-amine

[0250] 1H NMR (400 MHz, $DMSO-d_6$) δ 10.03 (s, 1H), 8.84 (d, $J = 5.4$ Hz, 1H), 8.64 (d, $J = 7.8$ Hz, 1H), 8.60 (d, $J = 8.3$ Hz, 1H), 8.34 (d, $J = 4.9$ Hz, 1H), 8.21 (d, $J = 7.8$ Hz, 1H), 8.11 (dt, $J_1 = 7.4$ Hz, $J_2 = 1.5$ Hz, 1H), 7.82-7.90 (m, 3H), 7.64-7.67 (m, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.02-7.06 (m, 1H); MS m/z : 300 ($M + 1$).

EXAMPLE 19

Preparation of the metal complex 30

19.1 Synthesis

[0251] 0.1 mL of 1.0 M $FeClO_4$ in ether is added to a solution of 0.2 mmol of **20** in EtOH at 60 °C. A white precipitate forms immediately. To this mixture is added 0.06 mL of triethyl amine and the resulting mixture is stirred for 20 min. After the mixture is cooled to rt, the white precipitate is filtered to yield **30**.

EXAMPLE 20

20.1 Assay for Compound Activity Towards hSK Channels

[0252] Cells expressing small conductance, calcium activated potassium channels, such as SK-like channels were loaded with $^{86}Rb^+$ by culture in media containing $^{86}RbCl$. Following loading, the culture media was removed and the cells were washed in EBSS to remove residual traces of $^{86}Rb^+$. Cells were preincubated with the drug (0.01 to 30 μM in EBSS) and then $^{86}Rb^+$ efflux was stimulated by exposing cells to EBSS solution supplemented with a calcium ionophore, such as ionomycin, in the continued presence of the drug. After a suitable efflux period, the EBSS/ionophore solution was removed from the cells and the $^{86}Rb^+$ content was determined by Cherenkov counting (Wallac Trilux). Cells were then

lysed with a SDS solution and the $^{86}\text{Rb}^+$ content of the lysate was determined. Percent $^{86}\text{Rb}^+$ efflux was calculated according to the following equation:

$$(\text{Rb}^+ \text{ content in EBSS} / (\text{Rb}^+ \text{ content in EBSS} + \text{Rb}^+ \text{ content of the lysate})) \times 100$$

20.2 Results

[0253] Compounds tested in this assay, along with their hSK2 inhibitory activity, are provided in Table 1.

Table 1

Compound Name	hSK2 Inhibitory Activity
(4-Methyl-pyridin-2-yl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine	++++
N ² -(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-pyridine-2,5-diamine	++++
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(5-pyrrolidin-1-yl-pyridin-2-yl)-amine	++++
1-[6-(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-ylamino)-pyridin-3-yl]-pyrrolidin-2-one	++++
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(5-thiophen-2-yl-pyridin-2-yl)-amine	++++
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(4-methyl-3,4,5,6-tetrahydro-2H-[1,3]bipyridinyl-6'-yl)-amine	++++
(5-Methoxy-pyridin-2-yl)-(5-methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-amine	++++
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(5-thiophen-3-yl-pyridin-2-yl)-amine	++++
Pyridin-2-yl-(4-pyridin-2-yl-pyrimidin-2-yl)-amine	++++
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(4-methyl-pyridin-2-yl)-amine	++++
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-pyridin-2-yl-amine	+++
(5-Chloro-pyridin-2-yl)-(5-methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-amine	+++
(5-Chloro-pyridin-2-yl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine	+++
N ² -(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-N5,N5-dimethyl-pyridine-2,5-diamine	+++
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(5-phenyl-pyridin-2-yl)-amine	+++
(5-Phenyl-pyridin-2-yl)-(4-pyridin-2-yl-pyrimidin-2-yl)-amine	+++
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine	+++
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-[5-(5-methyl-furan-2-yl)-pyridin-2-yl]-amine	+++

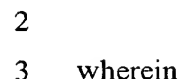
Compound Name	hSK2 Inhibitory Activity
[5-(3-Fluoro-phenyl)-pyridin-2-yl]-(5-methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-amine	+++
(5-Fluoro-pyridin-2-yl)-(5-methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-amine	+++
Pyridin-2-yl-(2-pyridin-2-yl-quinazolin-4-yl)-amine	+++
4-Chloro-2,6-di-pyridin-2-yl-pyrimidine	++
[2-(6-Methyl-pyridin-2-yl)-pyrimidin-4-yl]-pyridin-2-yl-amine	++
(5-Chloro-pyridin-2-yl)-(2-pyridin-2-yl-pyrimidin-4-yl)-amine	++
[4-(6-Methyl-pyridin-2-yl)-pyrimidin-2-yl]-pyridin-2-yl-amine	++
(6-Methyl-2-pyridin-2-yl-pyrimidin-4-yl)-pyridin-2-yl-amine	+
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(5-nitro-pyridin-2-yl)-amine	+
(4-Pyridin-2-yl-pyrimidin-2-yl)-(5-trifluoromethyl-pyridin-2-yl)-amine	+
N-(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-N'-pyridin-2-yl-hydrazine	+
(5-Bromo-pyridin-2-yl)-(5-methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-amine	+
Methyl-pyridin-2-yl-(4-pyridin-2-yl-pyrimidin-2-yl)-amine	+
Pyridin-2-yl-(4-pyridin-2-yl-quinazolin-2-yl)-amine	+
(5-Methoxy-2-pyridin-2-yl-pyrimidin-4-yl)-(5-trifluoromethyl-pyridin-2-yl)-amine	+
(5-Chloro-6-methyl-2-pyridin-2-yl-pyrimidin-4-yl)-(5-trifluoromethyl-pyridin-2-yl)-amine	+
(2,6-Di-pyridin-2-yl-pyrimidin-4-yl)-pyridin-2-yl-amine	+
(2,6-Di-pyridin-2-yl-pyrimidin-4-yl)-(5-trifluoromethyl-pyridin-2-yl)-amine	+

Key: + indicates $30\text{ }\mu\text{M} > \text{IC}_{50} > 5.0\text{ }\mu\text{M}$; ++ indicates $5.0\text{ }\mu\text{M} > \text{IC}_{50} > 1.0\text{ }\mu\text{M}$;

+++ indicates $1.0\text{ }\mu\text{M} > \text{IC}_{50} > 0.1\text{ }\mu\text{M}$; ++++ indicates $0.1\text{ }\mu\text{M} > \text{IC}_{50} > 0.0\text{ }\mu\text{M}$.

[0254] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

1 1. A compound having a structure according to Formula I:



4 A and B are independently substituted or unsubstituted 5- or 6- membered
5 heterocycloalkyl, or substituted or unsubstituted 5- or 6- membered
6 heteroaryl.

7 W^1 is $\begin{array}{c} \text{---C=} \\ | \end{array}$ or $\begin{array}{c} \text{---N---} \\ | \end{array}$;

8 W² is -CH=, -NH-, -N=, or -O-;

9 Z^1 is $-\text{C}=\text{C}-$, $-\text{N}-$, or $-\text{N}^{\oplus}=\text{N}-$;

10 Z^2 is -CH=, -NH-, -N=, or -O-;

11 X is a bond, -CH₂-, or -NR⁴-;

12 Y is a bond, -CH=N-NH-, -NH-CH₂-, or -NR⁵-;

13 s and t are independently integers from 1 to 4;

14 k is an integer from 1 to 2;

15 R¹, R², and R³ are independently H, -OH, -NO₂, -SO₂NH₂, halogen,
16 substituted or unsubstituted alkyl, substituted or unsubstituted
17 heteroalkyl, substituted or unsubstituted 3- to 7- membered cycloalkyl,
18 substituted or unsubstituted 5- to 7- membered heterocycloalkyl,
19 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,
20 or -NR⁷R⁸, wherein

21 R⁷ and R⁸ are independently H, halogen, substituted or unsubstituted
22 alkyl, substituted or unsubstituted heteroalkyl, substituted or
23 unsubstituted 5- to 7- membered cycloalkyl, substituted or
24 unsubstituted 5- to 7- membered heterocycloalkyl, substituted or
25 unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein
26 R⁷ and R⁸ are optionally joined together with the nitrogen to which
27 they are attached to form a substituted or unsubstituted 5- to 7-

28 membered heterocycloalkyl, or substituted or unsubstituted
29 heteroaryl; and
30 R⁴ and R⁵ are independently H, substituted or unsubstituted alkyl, substituted
31 or unsubstituted heteroalkyl, substituted or unsubstituted 3- to 7-
32 membered cycloalkyl, substituted or unsubstituted 5- to 7- membered
33 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
34 unsubstituted heteroaryl;
35 wherein if s is greater than one, then each R¹ is optionally different;
36 wherein if k is two, then each R² is optionally different;
37 wherein if t is greater than one, then each R³ is optionally different;
38 wherein two R¹ groups are optionally joined together with the atoms to
39 which they are attached to form a substituted or unsubstituted ring;
40 wherein two R² groups are optionally joined together with the atoms to
41 which they are attached to form a substituted or unsubstituted ring; and
42 wherein two R³ groups are optionally joined together with the atoms to
43 which they are attached to form a substituted or unsubstituted ring.

1 2. The compound of claim 1, wherein A is substituted or unsubstituted
2 pyridinyl.

1 3. The compound of claim 1, wherein B is substituted or unsubstituted
2 pyridinyl.

1 4. The compound of claim 1, wherein R¹, R², and R³ are independently
2 H, -NH₂, -NO₂, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted
3 heteroalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or
4 unsubstituted aryl, or substituted or unsubstituted heteroaryl.

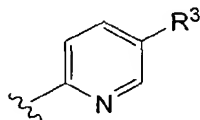
1 5. The compound of claim 4, wherein
2 R¹ is H, substituted or unsubstituted alkyl, substituted or unsubstituted
3 heteroalkyl, or substituted or unsubstituted aryl;
4 R² is H, halogen, substituted or unsubstituted alkyl, substituted or
5 unsubstituted heteroalkyl, substituted or unsubstituted 5- to 7- membered
6 heterocycloalkyl, or substituted or unsubstituted aryl;

7 R^3 is H, $-NH_2$, $-NO_2$, halogen, substituted or unsubstituted alkyl, substituted
 8 or unsubstituted heteroalkyl, substituted or unsubstituted aryl, or
 9 substituted or unsubstituted heteroaryl.

1 6. The compound of claim 5, wherein
 2 R^1 is H, methyl, $-NH_2$, or unsubstituted phenyl;
 3 R^2 is H, Cl, methyl, $-OCH_3$, or unsubstituted pyridinyl; and
 4 R^3 is H, $-NH_2$, $-NO_2$, Cl, Br, F, methyl, phenyl, fluorophenyl,
 5 $-CF_3$, $-OCH_3$, dimethylamino, unsubstituted piperidine, *p*-methyl
 6 morpholino, unsubstituted pyrrolidinonyl, unsubstituted 2-thiophenyl,
 7 unsubstituted 3-thiophenyl, unsubstituted furanyl, or *n*-methyl
 8 piperizinyl.

1 7. The compound of claim 2, wherein X is a bond, k is 2, and R^2 is H or
 2 $-OCH_3$.

1 8. The compound of claim 7, wherein Y is $-NH-$, t is 1, and B is



2
 3 wherein

4 R^3 is H, $-NH_2$, $-NO_2$, halogen, substituted or unsubstituted alkyl, substituted
 5 or unsubstituted heteroalkyl, substituted or unsubstituted 3- to 7-
 6 membered cycloalkyl, substituted or unsubstituted 5- to 7- membered
 7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 8 unsubstituted heteroaryl.

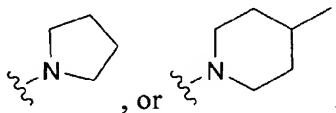
1 9. The compound of claim 8, wherein R^3 is Cl or
 2 $-NR^7R^8$,

3 wherein

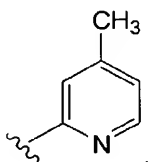
4 R^7 and R^8 are independently H, halogen, substituted or unsubstituted alkyl,
 5 substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 6 5- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7-
 7 membered heterocycloalkyl, substituted or unsubstituted aryl, or
 8 substituted or unsubstituted heteroaryl, wherein R^7 and R^8 are

optionally joined together with the nitrogen to which they are attached to form a substituted or unsubstituted 5- to 7- membered heterocycloalkyl, or substituted or unsubstituted heteroaryl.

10. The compound of claim 9, wherein R^3 is Cl, $-NH_2$, $-N(CH_3)_2$,

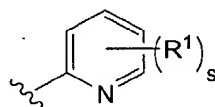


11. The compound of claim 7, wherein Y is $-NH-$ and B is



12. The compound of claim 3, wherein Y is a bond, k is 1 and R^2 is H.

13. The compound of claim 12, wherein X is $-NH-$ and A is



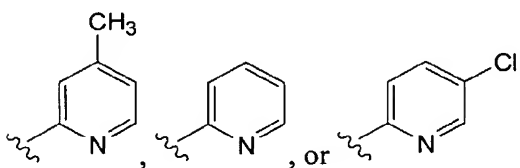
(III)

wherein

s is an integer from 1 to 4; and

R^1 is H, halogen, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 5- to 7- membered cycloalkyl, substituted or unsubstituted 5- to 7- membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

14. The compound of claim 13, wherein A is



1 **15.** A metal complex, comprising a polyvalent metal ion and a
2 polydentate component of a metal ion chelator, wherein said polydentate component is a
3 compound according to claim 1.

1 **16.** The complex of claim 15, wherein said polyvalent metal ion is
2 selected from iron, zinc, copper, cobalt, manganese, and nickel.

1 **17.** A method of decreasing ion flow through potassium ion channels in a
2 cell, said method comprising contacting said cell with a potassium ion channel-modulating
3 amount of a compound of one of claims 1-14 or a metal complex of one of claims 15 or 16.

1 **18.** The method according to claim 17, wherein said potassium ion
2 channel comprises at least one SK subunit.

1 **19.** A method of treating a disease through modulation of a potassium ion
2 channel, said method comprising administering to a subject in need of such treatment, an
3 effective amount of a compound of one of claims 1-14 or a metal complex of one of claims
4 15 or 16.

1 **20.** The method according to claim 19, wherein said disorder or condition
2 is selected from central or peripheral nervous system disorders, gastroesophageal reflux
3 disorder, gastrointestinal hypomotility disorders, irritable bowel syndrome, secretory
4 diarrhea, asthma, cystic fibrosis, chronic obstructive pulmonary disease, rhinorrhea,
5 convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney
6 disease, bladder spasms, urinary incontinence, bladder outflow obstruction, ischemia,
7 cerebral ischemia, ischemic heart disease, angina pectoris, coronary heart disease,
8 Reynaud's disease, intermittent claudication, Sjorgren's syndrome, arrhythmia,
9 hypertension, myotonic muscle dystrophy, xerostomi, diabetes type II, hyperinsulinemia,
10 premature labor, baldness, cancer, and immune suppression.

1 **21.** The method according to claim 20, wherein said central or peripheral
2 nervous system disorder comprises migraine, ataxia, Parkinson's disease, bipolar disorders,
3 trigeminal neuralgia, spasticity, mood disorders, brain tumors, psychotic disorders,
4 myokymia, seizures, epilepsy, hearing and vision loss, psychosis, anxiety, depression,
5 dementia, memory and attention deficits, Alzheimer's disease, age-related memory loss,

6 learning deficiencies, anxiety, traumatic brain injury, dysmenorrhea, narcolepsy and motor
7 neuron diseases.

1 **22.** A pharmaceutical composition comprising a pharmaceutically
2 acceptable carrier and a compound of one of claims **1-14** or a metal complex of one of
3 claims **15** or **16**.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US2005/012696

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/506 C07D401/14 A61P25/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K C07D A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/39101 A (ASTRAZENECA UK LIMITED; BRADBURY, ROBERT, HUGH; BREAUULT, GLORIA, ANNE;) 6 July 2000 (2000-07-06) claims 1-10,14; example 223 -----	1-14,22
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 23 August 2005		Date of mailing of the international search report 01/09/2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Stroeter, T

INTERNATIONAL SEARCH REPORT

Int Application No
PCT/US2005/012696

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/012696

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-21 are (at least partly) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/US2005/012696

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